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RESEARCH ARTICLE

Comparative Proximate Composition of Selected Cultivars of Bitter Gourd (*Momordica charantia*) Fruit through its Flour Formation

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ABSTRACT

Background: The proximate analysis is crucial to ascertain more desirable cultivars with abundant chemical constituents to be used against numerous diseases.
Objective: Purpose of this study was to determine the proximate composition of six cultivars of bitter gourd (*Momordica charantia* L.) viz., Black King, GHBG-1, KHBG-1, FSD Long, BG 20, and Noor for use as flour.
Methodology: The whole fruit (with peel and seeds), and skin, flesh, seeds were dried separately and grind to obtain fine flour. All the determinations were made in triplicate and data of all the cultivars were compared for various parameters.
Results: The high moisture contents were observed in flesh part of cultivar BG 20 (9.07±0.55%) while the least moisture contents were found in seeds of GHBG-1 (5.20±0.30%). The flesh was rich in ash and protein contents. The least protein contents were observed in the seeds of KHBG-1 with value of 9.06%. Different cultivars of bitter gourd and fruit showed significant differences regarding crude fat contents. The maximum crude fiber contents were observed in seeds of different cultivars *i.e.*, 21.42 (BG 20), 19.07 (Black King), 18.89 (Noor), 18.7 (GHBG-1), 17.11(KHBG-1), and 16. 51 (FSD Long). The fruit skin had the highest amount of nitrogen free extract [72.34 (BG 20), 67.6 (Black King), 61.09 (FSD Long), 69.76 (KHBG-1), 58.0 (GHBG-1) and 57.28 (Noor)] followed by flesh part (70.29, 65.27, 56.62, 68.25, 56.82 and 56.13%, respectively).
Conclusion: proximate composition of flour of bitter gourd fruit showed that different cultivars and fruit parts showed remarkable differences regarding different nutritional components. Black King cultivar was more promising followed by FSD Long and BG 20. It is suggested that flour of these cultivars should be further analyzed for phytonutrient and biochemical evaluation.

INTRODUCTION

The regular consumption of vegetables is essential to maintain human health as these have bevy of chemical compounds that have nutritional as well as medicinal properties. Many disorders are related to inadequate consumption of vegetables. The intake of a specific food may assuage several types of ill effects due to modulatory effects of chemicals moieties present in them. Dietary interventions may help reduce the chances of onset of diseases and reduce the severity of symptoms associated with diseases. The bitter gourd (*Momordica charantia* L.), a member of the family Cucurbitaceae. It is a thin vine, produces fruit in summer season which is bitter in taste (Yan *et al.* 2019) and reported to have a role in mitigation of several lifestyle-related disorders.

In recent years, many studies highlighted the potential of bitter gourd fruit in reducing cholesterol (Bano *et al.* 2011; Tayyab *et al.* 2012; Tayyab and Lal 2013), visceral fat mass (Chen *et al.* 2012), blood glucose level (Paul and Raychaudhuri 2010; Fuangchana *et al.* 2011; Wehash *et al.* 2012; Tayyab and Lal 2013), and cellular proliferations in cancer (Ray *et al.* 2010; Manoharan *et al.* 2014), as well as provide positive impact against HIV and neurodegenerative

diseases (Fang and Ng 2011). The diverse chemicals present in this plant impart anti-tumor, antioxidative, anti-hyperlipidemic, anti-diabetic, anti-mutagenic, anti-inflammatory, anti-ulcerogenic, and immune-modulatory activities (Islam *et al.* 2011; Gill *et al*. 2012; Lu *et al*. 2012; Mohammady *et al.* 2012; Joseph and Jini 2013; Chao *et al*. 2014; Majumda and Debnath 2014). These wide ranges of benefits are due to the presence of diverse chemicals in different parts of its fruit.

To explore a more desirable variety with suitable chemical composition, proximate analysis is crucial. Such a chemical analysis provides a basis to determine the presence of antioxidants, nutrients, phytochemicals, and resultant physiological functions. Moreover, nutritional status and overall composition are important criteria to determine beneficial aspects of any ingredient used as food. Furthermore, chemical composition is critically important for the development of designer foods. As bitter gourd is a natural source of vital chemicals, it can be used as a functional food to benefit health (Lee *et al.* 2013). The peel and seeds of this fruit are considered inedible, although its skin is a rich source of minerals, lipids, proteins, and fibres (Andrade *et al.* 2023). The seeds are also a reservoir of many macro- and micronutrients such as proteins, carbohydrates, minerals, bioactive compounds, and vitamins. The chemicals present in the skin and seeds of bitter gourd might be a good source of bioactive components to boost health and provide protection against wide ranging human malignancies (Singla *et al.* 2023).

Some previous studies explored the chemical composition of leaf, fruit, and pericarp of bitter gourd in different geological regions of the world (Bakare *et al.* 2010; Horax *et al.* 2010; Saeed *et al.* 2018). As different cultivars are genetically diverse, the present research is planned to assess the comparative proximate composition of fruit and its parts in different lines grown in similar climatic, geographical and agronomical conditions.

MATERIALS AND METHODS

Procurement of bitter gourd materials

In the present study, proximate composition of six cultivars of bitter gourd (*Momordica charantia* L.) viz., Black King, GHBG-1, KHBG-1, FSD Long, BG 20, and Noor was made (Fig. 1). The fruits of selected cultivars were procured from Ayub Agricultural Research Institute, Faisalabad-Pakistan. The selection of cultivar was based on yield and other quality attributes (freshness, not fully mature etc.).

Handling of materials

The fruits of selected cultivars were washed with water to remove soil particles, adhered dust, or other undesirable objects. The fruits were dried at room temperature for a few hours. The skin of the fruit was peeled. The fruits were cut open to remove the seeds. The remaining fruit was cut to small sized pieces. After cutting whole fruit (with peel and seeds), small slices were obtained (Fig. 2). The whole fruit and its parts (skin, flesh, seeds) for each cultivar were collected separately in plastic jars. These fruit parts and whole fruit were dried in sunlight till dried completely except retaining small proportion used to determine moisture contents. The dried fruit parts and whole fruits of different cultivars were ground with the help of a small laboratory grinder. The powder obtained after grinding was sieved to obtain fine flour. The coarse powder was grinded again to refine further. The fine flour was stored separately in labelled air-tight polythene bags to be used for further analysis.

Proximate analysis

The fruit of different cultivars and parts were analyzed for proximate composition using the methods given below.

Moisture content: To determine moisture contents, 3g of sample was dried at 105±5ºC using hot air oven following Method No. 44-01 (AACC 2000). The drying continued until the constant weight of the sample was obtained. Following formula was used to calculate moisture contents in fruit of different cultivars and parts:

$$\text{Moisture contents } \% = \frac{W1 - W2}{W1} \times 100$$

Where W1 is the weight of fresh sample and W2 is weight of dry sample.

Ash content: The AACC Method No. 08-01was used to determine the ash contents. The sample was incinerated directly in crucible (AACC 2000). Then the crucible was heated on oxidizing flame. The fumes gradually disappeared while heating continuously. Then, muffle furnace (MF-1/02, Pakistan) was used to ignite at 550 ˚C temperature till gray white residues appeared. Following formula was applied to calculate ash contents:

$$\text{Ash content } (\%) = \frac{W1}{W0} \times 100$$

Where W1 is weight of dry sample (g) and W0 is the weight total sample (g)

Crude protein: The nitrogen contents were estimated using Kjeltech Equipment (Model number: 808, Behr Dusseldort) following the procedure described in Method No. 46-13 (AACC 2000). The digestion mixture (K_2SO_4:$FeSO_4$:$CuSO_4$ in the ratio of 10:5:85) and concentrated H_2SO_4 were used to digest the samples repeatedly after every 3 h until transparent or light green color appeared. The material after digestion was obtained and diluted with 250 mL of water. In distillation apparatus, 10 mL of 40% NaOH solution was taken to distill 10 mL of diluted sample. Liberation of ammonia started, which was estimated using methyl red indicator in 4% boric acid solution. Lastly, the titration of this distillate using 0.1 N H_2SO_4 was performed till golden brown color appeared. Following formula was used to

Fig. 1: Fruits of different cultivars of bitter gourd used in this study

Fig. 2: Fruit and its components

determine presence of crude protein (%) based on the N content of the sample:

$$N\,(\%) = \frac{V1 \times V2 \times 0.0014}{W0 \times V3} \times 100$$

$$\text{Crude protein}(\%) = 6.25 \times N\,(\%)$$

Where W0=weight of sample, V1=Volume of 0.1 normal H_2SO_4 (mL), V2= Volume of dilution (g), V3= Volume of sample before dilution (mL)

Crude fat: To analyze crude fat contents in the sample (Method No. 30-10), 3g of flour was taken in solvent (n-hexane) using Soxhlet Apparatus (AACC 2000):

$$\text{Crude fat \%} = \frac{W1}{W0} \times 100$$

Where W1= weight of fat (g) and W0 is the weight of plant sample (g).

Crude fiber: To estimate crude fiber in the sample, simultaneous digestion with H_2SO_4 (1.25%) and NaOH (1.25%) solutions was carried out. Labconco Fibertech (USA) was used for determination of crude fiber contents in the sample. The ignition of sample at 550ºC in muffle furnace had resulted in formation of white residues. Method No. 32-10 was used to determine percentage of fiber in sample (AACC 2000). The following expression was used to calculate the crude fiber content:

$$\text{Crude fiber \%} = \frac{W1}{W0} \times 100$$

Where W1= weight loss on ignition (g), W0 is the weight of plant sample (g).

Nitrogen free extracts (NFE): The NFE in sample is determined by using the sum of all percentages of nutrients and subtracting from 100 (McClement *et al.* 2021), as given below:

NFE (%) = 100 – (% ash + % crude protein + % crude fat + % crude fiber)

Data analysis

Data were analyzed to find differences among the cultivars and their respective parts using Statistix v.8.1. The graphical presentation of the data was made using MS Excel 365.

Chemicals

The chemicals used to analyze proximate composition were of analytical grade and purchased from Sigma-Aldrich, Japan, Cayman, Europe and Merck.

RESULTS

Different chemical attributes of selected bitter gourd cultivars and fruit parts showed significant differences in different parameters (Fig. 3a). The flesh part has higher moisture contents in all cultivars *i.e.*, 9.07 (BG 20), 8.1 (KHBG-1), 7.63 (FSD Long), 7.63 (Noor), 7.6 (Black King), and 7.43 (GHBG-1). The seeds were found to possess low moisture contents i.e., 6.23 (BG 20), 5.93 (Black King), 5.63 (FSD Long), 6.17 (KHBG-1), 5.2 (GHBG-1), and 5.73 (Noor). The moisture contents in skin of different cultivars were 7.97 (BG 20), 6.9 (Black King), 6.4 (FSD Long), 6.77 (KHBG-1), 6.6 (GHBG-1) and 6.87 (Noor). The high moisture contents were also observed in whole fruit with values of 8.00 (BG 20), 7.03 (Black King), 7.37 (FSD Long), 7.1 (KHBG-1), 6.6 (GHBG-1) and 7.27 (Noor).

It was obvious from results that flesh part is rich in ash contents (Fig. 3b) i.e., 2.86, 4.39, 3.6, 3.71, 2.37, and 2.06% followed by skin (2.72, 3.18, 3.1, 2.81, 2.09 and 2.34%), whole fruit (2.39, 3.33, 3.23, 2.98, 2.13 and 1.88% and seeds (1.31, 1.83, 1.87, 1.41, 1.19 and 1.11%) for BG 20, Black King, FSD Long, KHBG-1, GHBG-1 and Noor respectively.

Results regarding crude protein contents in different cultivars of bitter gourd (Fig. 3c) indicated that flesh part of cultivar Noor, FSD Long, and GHBG-1 possess high protein contents i.e., 33.14, 30.53 and 30.07, respectively. The protein contents in flesh part of other cultivars were 16.52, 17.87 and 18.29 for BG 20, Black King and KHBG-1 respectively. The least protein contents were observed in the seeds of KHBG-1 with value of 9.06 % while seeds of cultivar FSD Long had the highest crude protein content (14.47%).

Different cultivars of bitter gourd and fruit parts showed significant differences regarding crude fat contents (Fig. 3d). The results indicated that seeds of different cultivars are rich in crude fat contents (%) i.e., 14.19 (BG 20), 14.28 (Black King), 11.48 (FSD Long), 13.5 (KHBG-1), 9.23 (GHBG-1), and 10.15 (Noor). The least amount of fat was found in the skin part of cultivar Noor (6.42%).

As presented in Fig. 3e, the maximum crude fiber contents were observed in seeds of different cultivars *i.e.*, 21.42 (BG 20), 19.07 (Black King), 18.89 (Noor), 18.7 (GHBG-1), 17.11(KHBG-1), and 16. 51 (FSD Long). The comparative low amount of fiber contents were observed in skin [(2.24 (BG 20), 3.81 (Black King), 1.21 (FSD Long), 2.34 (KHBG-1), 1.55 (GHBG-1), and 1.86 (Noor)] and flesh [(3.83 (BG 20), 4.02 (Black King), 1.84 (FSD Long), 2.28 (KHBG-1), 2.33 (GHBG-1), and 2.15 (Noor)].

Fig. 3f depicted that amounts of NFE were remarkably different in different parts and cultivars. The skin part of fruit displayed the highest amount of NFE [(72.34 (BG 20), 67.6 (Black King), 61.09 (FSD Long), 69.76 (KHBG-1), 58.0 (GHBG-1), and 57.28 (Noor)] followed by flesh part (70.29 (BG 20), 65.27 (Black King), 56.62 (FSD Long), 68.25 (KHBG-1), 56.82 (GHBG-1), and 56.13% (Noor)). The NFE (%) in whole fruit of different cultivars were found to be 68.15% (BG 20), 62.9% (Black King), 54.28% (FSD Long), 64.23% (KHBG-1), 57.39% (GHBG-1) and 57.53% (Noor).

DISCUSSION

The results of the current study indicated low values of moisture contents. These low values are important to protect the flour from microbial contamination or spoilage and to enhance the storage period. Hussain *et al.* (2024) also reported that peel, flesh and seeds of bitter gourd possess lesser amount of moisture contents with values of 6.10, 7.10 and 4.88, respectively. In a similar way, Gayathri (2014) found low moisture contents (6.14%) in bitter gourd fruit. In another study, Aslam *et al*. (2013) also found low moisture contents (4.71%) in bitter gourd fruit. Similarly, Saeed *et al*. (2010) analyzed bitter gourd flakes, peel, and seed for moisture contents and found moisture contents of 4.72, 4.15

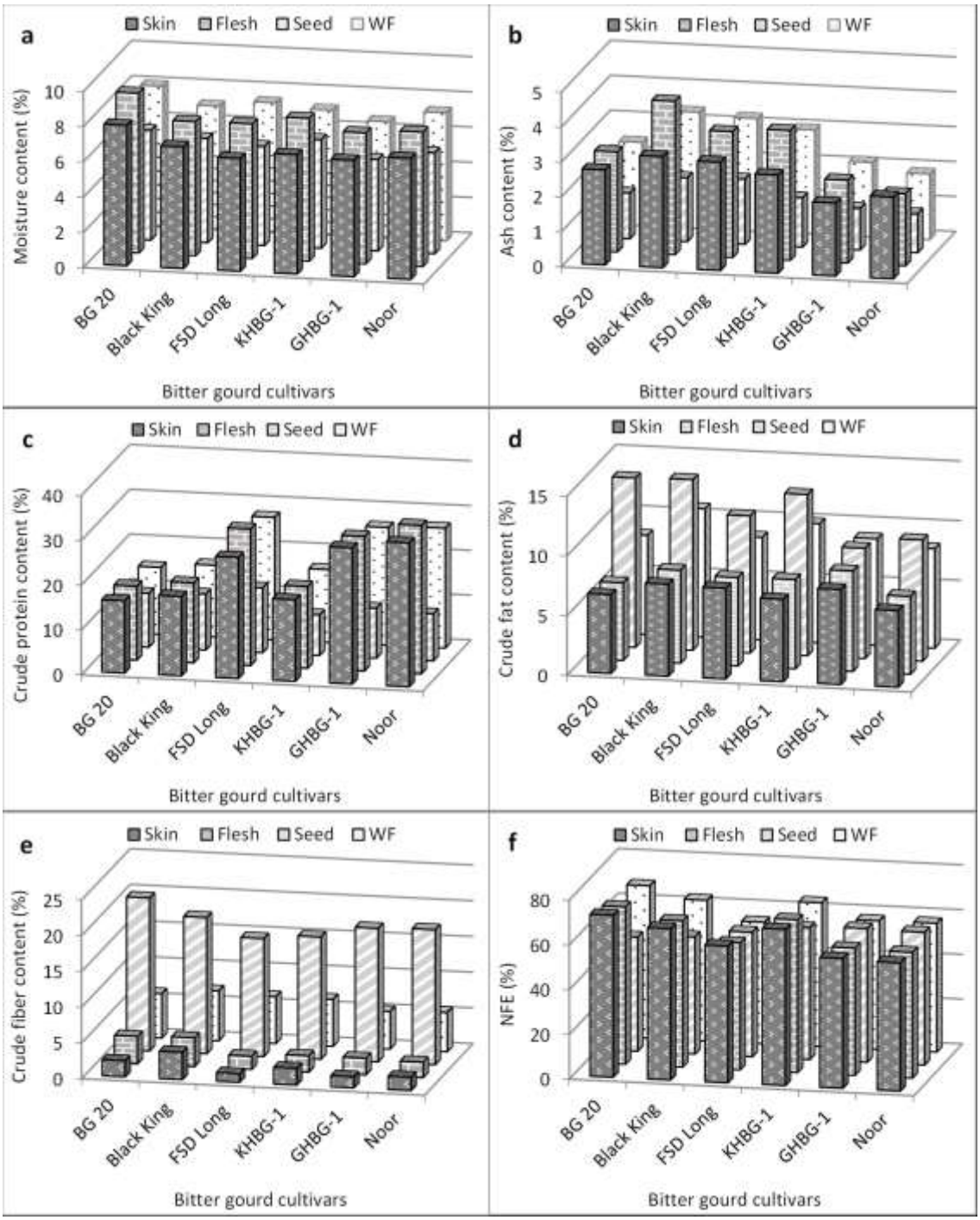

Fig. 3: Proximate analysis of parts of different cultivars bitter gourd: (a) moisture contents, (b) ash contents, (c) crude proteins, (d) crude fat contents, (e) crude fiber contents and (f) nitrogen free extract (NFE) contents.

and 4.09%, respectively. Bakare *et al*. (2010) reported higher moisture contents in seeds (20.69%) and low (10.74%) in fruit of bitter gourd. Low moisture contents (8.06%) were also detected by Hussain *et al*. (2009) in dried fruit samples of bitter gourd. Mathew *et al*. (2014) also found low moisture contents (7.00%) in bitter gourd seeds. Ali *et al*. (2008) studied three bitter gourd cultivars and revealed that the seeds of these cultivars had low moisture contents (7.62 to 8.20%). Contrary to these findings, Anjum *et al*. (2013) observed higher moisture contents in two bitter gourd cultivars *i.e*., 29.32 and 22.91%. Furthermore, very high moisture contents were observed by Ullah *et al*. (2011)

in four bitter gourd that ranged between 91.6 to 92.92%. Islam *et al.* (2011) also stated high moisture contents in flesh (92.4 to 93.5%) and seeds (53 to 75%). Very high values for moisture contents in certain experiments were due to use of fresh fruit samples for analysis.

The ash reflects the existence of minerals present in any plant part. In the present study, different cultivars showed considerable amount of ash contents in whole fruit and fruit parts. Hussain *et al.* (2024) found abundant ash contents in peel (6.26%), flesh (4.45%) and seeds (5.40%). Gayathri (2014) revealed that bitter gourd fruit possessed ash contents (2.76%). Contrary to this, Bangash *et al.* (2011) found 0.90% ash content in bitter gourd fruit. In a similar way, Ullah *et al.* (2011) revealed that bitter gourd had low ash content (0.75–1.20%). Contrary to these findings, Saeed *et al.* (2010) observed remarkably high ash contents in flakes, peel, and seeds with values of 6.43, 14.99 and 4.56%, respectively. They also illustrated variable amounts of ash in different components of bitter melon fruit. Similarly, Hussain *et al.* (2009) reported high ash contents (8.96±0.01) in fruits of vegetables. Mathew *et al.* (2014) investigated seeds of bitter gourd and found ample amount of ash (4.00%). Bakare *et al.* (2010) reported ash contents with values of 9.73 and 7.36% for seeds and fruit, respectively.

The results highlighted that protein contents were higher in bitter gourd in this study. Hussain *et al.* (2009) also reported 21.12% protein contents in bitter gourd fruit. A comparable protein contents in bitter gourd fruit (15.56%) was also reported by Aslam *et al.* (2013). Similarly, bitter gourd flakes and peel examined by Saeed *et al.* (2010) indicated 20.66 and 20.37% protein contents, respectively. They also reported that seeds of bitter gourd are valuable source of protein (19.01%). Similarly, high amount of protein (19.50%) was observed by Mathew *et al.* (2014). Anjum *et al.* (2013) examined that protein values showed significant differences due to selection of different bitter gourd cultivars. They observed 19.17 and 14.92% protein contents in the seeds of two different cultivars. Ullah *et al.* (2011) assessed low values (1.17–2.4%) for protein contents in the selected cultivars. Similarly, Hussain *et al.* (2024) found low protein contents (2.37–3.40%) in different parts of bitter gourd. Gayathri (2014) reported higher values (27.88%) for crude proteins in fruit. Many of these studies highlighted that protein contents were higher in flesh or edible portion while in some studies, protein contents were high in seeds (Islam *et al.* 2011). In different cultivars, protein contents differ widely, and it was observed that dark green varieties are low in protein contents than light green cultivars (Islam *et al.* 2011).

The present findings regarding crude fat contents are verified by study outcomes of Bakare *et al.* (2010) which depicted comparable crude fat contents of 6.11% in flesh and 11.50% in seeds. However, Saeed *et al.* (2010) observed low values of crude fat in flakes, seeds and peel with values of 0.25, 5.24 and 0.18%, respectively. Similarly, Hussain *et al.* (2024), reported that fat contents in bitter gourd peel, fruit and seeds were 1.03, 1.34 and 3.50%, respectively. On the other hand, Mathew *et al.* (2014) observed that seeds contained an abundant quantity of crude fat (34%). Aslam *et al.* (2013) reported high amount of fat (26.67%) in bitter gourd fruit. Different cultivars showed remarkable differences regarding lipid contents (Ali *et al.* 2008). These results were alike the findings of this study.

The fiber contents are valuable for gastrointestinal health besides other functions (Gill *et al.* 2021). The bitter gourd fruit is a valuable source of dietary fiber. Due to high fiber contents, bitter gourd has potential to lower the onset of number of maladies such as cancer, hypertension, diabetes, obesity gastrointestinal disorder and associated complications (Saldanha 1995). The present results indicated high fiber contents in the seeds than other parts. Saeed *et al.* (2010) revealed that crude fiber in seeds was higher (22.46%) followed by peel and flakes with values of 17.77 and 17.08%, respectively. Similarly, Mathew *et al.* (2014) determined 12% crude fiber in bitter melon seeds. Gayathri (2014) reported 2.31% crude fiber contents in bitter gourd fruit. Low fiber contents were observed in bitter melon (1.4%) by Bangash *et al.* (2011). Another research reported high fiber contents in seeds of two selected bitter gourd cultivars (Anjum *et al.* 2013).

The NFE primarily represents carbohydrates in plant materials. Different fruit parts and cultivars showed abundant quantity of NFE. The current results are also supported by Saeed *et al.* (2010) who observed high NFE in flakes (50.86%), peel (42.54%), and seed (44.64%). Gayathri (2014) also studied high carbohydrate contents (85.41 mg/100g) in fruit of bitter gourd. Aslam *et al.* (2013) also showed that bitter gourd has 43.20% carbohydrate content. Likewise, Hussain *et al.* (2009) found high amount of NFE (56.02%) in bitter gourd fruit. Slightly low values (32.51–35.52) for NFE have been reported in different bitter gourd cultivars (Ali *et al.* 2008). The reason behind these variations is genetic diversity in cultivars, impact of abiotic factors, stages of fruit maturity, agro-climatic conditions and post-harvesting conditions.

CONCLUSIONS

The different parameters related to proximate composition of flour of bitter gourd fruit showed that different cultivars and fruit parts showed remarkable differences regarding different nutritional components. The chemical composition is crucial in development of functional or designer foods. The results revealed that Black King cultivar proved the most promising followed by FSD Long and BG 20. It is recommended that these cultivars should be further analyzed for phytonutrient and biochemical evaluation.

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AUTHOR CONTRIBUTIONS

M, conceptualization and writing original draft; FS, overall supervision and data analysis; FN, visualization, review and editing.

CONFLICT OF INTEREST

The authors declared no conflict of interest

DATA AVAILABILITY

The data will be made available upon request to the author

ETHICS APPROVAL

Not applicable

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REVIEW ARTICLE

A Review of Drug-Induced Congenital Heart Defects: Teratogenicity, Mechanisms and Prevention Strategies

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ABSTRACT

Background: Congenital heart defects (CHDs) represent one of the most prevalent types of birth defects, affecting nearly 1% of live births globally. While genetic predispositions contribute to CHDs incidence, increasing evidence highlights the critical role of teratogenic drug exposure during pregnancy.
Objective: This review explores the teratogenic potential of various drug classes—including antiepileptics (valproic acid, phenytoin), isotretinoin, anticoagulants, Angiotensin-Converting Enzyme (ACE) inhibitors, and select antipsychotics—in disrupting fetal cardiac development.
Methodology: The information presented in this review was acquired from different databases including Google, Google Scholar, Elsevier, Wiley, Springer, Taylor & Francis, etc.
Results: The data have revealed that the mechanisms underlying drug-induced CHDs involve oxidative stress, disruption of cardiac signaling pathways, altered folate metabolism, and hemodynamic imbalances. Each agent exhibits unique pathophysiological pathways, such as histone deacetylase inhibition by valproic acid or retinoic acid (RA)-mediated gene dysregulation by isotretinoin, ultimately leading to structural heart anomalies. The review also outlines prevention strategies, emphasizing preconception counseling, alternative drug regimens, early screening, and rigorous pregnancy prevention programs.
Conclusion: As fatal birth threat, a comprehensive understanding of drug-related teratogenicity is crucial to ensuring maternal safety while minimizing fetal cardiovascular risks during gestation.

INTRODUCTION

Congenital heart defects (CHDs) are the abnormalities with the heart's structure that happen while a baby is developing in the womb, which can affect the heart's normal function due to a range of defects, which affect valves and blood vessels. CHDs are among the most common birth defects affecting nearly 1% of live births worldwide (Yang *et al.* 2024). Specific global data on the prevalence and mortality rates of congenital heart disease by gender for the years 2020 to 2024 is limited, but the most comprehensive data available currently only goes up to 2017. A systematic analysis for the Global Burden of Disease Study–2017 reported that in 2017, the global incidence rate of CHDs was 17.9 per 1,000 live births, with 19.1 per 1,000 for males and 16.6 per 1,000 for females (Ray *et al*. 2001; Sun *et al*. 2015). The age-standardized mortality rate (ASMR) for CHDs also decreased from 6.3 per 100,000 population in 1990 to 3.9 per 100,000 in 2017. Men generally had a slightly higher mortality rate than women during this time period. A study in the United States using data from 2017 to 2022 showed that the risk of death for patients with CHD was significantly higher during the COVID-19 pandemic as compared to the past years. The study also found that male CHDs patients had a higher risk of death (Cubeddu 2016).

Although the exact cause is not clearly known, the CHDs can be caused by genes, environmental factors, or when the mother is exposed to teratogenic factors during pregnancy. These defects can be minor and fix themselves or they can be very serious and need surgery(Frommeyer & Eckardt, 2016). Some CHDs are so minor that they go away on their own, while others are very serious and can even be life threatening. Early detection of CHDs has improved, thanks to advancements in diagnostic techniques such as fetal echocardiography. Survival rates have also increased significantly due to improvements in surgical and medical treatments. However, people with a congenital heart defect (CHD) often need lifelong medical follow-up to monitor and manage their condition (Li and Ramos 2017).

In teratogenicity, a drug that can cause birth defects in a baby while it is still developing fetus, and these drugs are called teratogens. They can disrupt the normal growth of baby by causing damage to the cells, interfering with how cells communicate with each other or cause stress to the cells (Taye *et al*. 2024). Many kinds of drugs can be teratogens including some drugs used to prevent seizures, address skin problems, and to prevent blood clots. If certain drugs are taken during pregnancy, they can increase the chances of a baby having a CHD.

Understanding how drugs can cause heart defects is very important for making sure that pregnant women get the best care while also keeping their babies safe (Wang *et al.* 2024). In this review, the information will be provided on how specific medications, especially antiepileptics, anticoagulants, retinoids and ACE inhibitors can lead to problems with a fatal heart development (Lewis-Israeli *et al.* 2021). Focus will be on what can be done to prevent the problems such as carefully assessing the risks of taking certain drugs during pregnancy, using different treatments when possible and making sure that doctors and pregnant women follow guidelines to minimize exposure to harmful drugs.

BRIEF MECHANISMS OF DRUG INDUCED CONGENITAL HEART DEFECTS

The CHDs result from multiple teratogenic mechanisms that disrupt normal cardiac development. The most important of the CHDs are discussed below (Table 1).

Oxidative stress and apoptosis

This occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. Some drugs like valproic acid and phenytoin can increase ROS production. This excess ROS can damage cells, leading to apoptosis or programmed cell death. When apoptosis occurs in the cells that are developing the heart, it can disrupt normal heart formation and lead to CHDs (Xuan *et al*. 2022).

Interference with cardiac signaling pathways

Signaling pathways that are essential for heart development. For example, retinoids can interfere with RA signaling, which is crucial for the migration of cardiac neural crest cells and the formation of the heart tube. Disruptions in these pathways can lead to conotruncal defects and malformations of the outflow tract, which is the part of the heart that pumps blood out to the body (Ho *et al.* 2022).

Folate metabolism disruption

Some medications such as valproic acid can interfere with folate metabolism. This can lead to folate deficiencies which are important for DNA synthesis and cell differentiation. Disruptions in these processes can contribute to both neural and cardiac defects including septal abnormalities (Thorat *et al.* 2024).

Altered hemodynamics

Certain medications such as ACE inhibitors can affect fetal hemodynamics. They can impair fetal kidney function which can reduce amniotic fluid volume and lead to reduced blood flow to the fetus. This hemodynamic instability can cause left-sided heart defects such as hypoplastic left heart syndrome(Nugraha *et al.* 2019).

COMPARING CORONARY HEART DISEASE RISK ACROSS DIFFERENT DRUG CLASSES

Cardiovascular disease, particularly CHD, is a leading cause of morbidity and mortality. Managing risk factors like hypertension and dyslipidemia is crucial in preventing CHD (Nugraha *et al.* 2018).

Among other medications, aspirin is a widely used antiplatelet medication for secondary CHD prevention. The Second Joint Task Force recommends aspirin (at least 75 mg) for coronary patients and those with cerebral atherosclerosis or peripheral disease. With statins and beta-blockers, it lowers all-cause mortality by 90%. Diabetes is a significant CHD risk factor. Managing blood glucose levels with anti-diabetic medications is crucial. However, some anti-diabetic drugs may increase cardiovascular risk, while others have a neutral or beneficial effect (Nugraha *et al.* 2018; Yang *et al.* 2024).

CONFLICTING EVIDENCE IN CHD RISK FACTORS

Several topics have sparked ongoing debates and conflicting evidence regarding their impact on coronary heart disease (CHD) risk. Important of these are briefly described below (Table 1).

Table 1: Different classes of medications causing CHD along with their mechanism, metabolic effects and severity

Medication Class	Mechanism of Increased CHD Risk	Metabolic Effects	Severity of Risk
Antipsychotics (Olanzapine, Clozapine, Risperidone)	- Weight gain - Dyslipidemia - Insulin resistance	Weight gain - Dyslipidemia (increased triglycerides, LDL, decreased HDL) - Insulin resistance (potential progression to type 2 diabetes)	Moderate to High Especially for second-generation antipsychotics (SGAs)
Corticosteroids (Prednisone, Dexamethasone)	Rheumatoid arthritis (RA) is a chronic inflammatory joint disease	Hypertension - Dyslipidemia (increased triglycerides, LDL) - Insulin resistance - Visceral fat deposition (abdominal obesity)	Moderate Especially with long-term use
NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)	Inhibition of COX-1 and COX-2 Endothelial Dysfunction	Altered Lipid Profiles High levels of LDL ("bad" cholesterol) and triglycerides promote atherosclerosis (plaque build-up in arteries), raising the risk of CHD. Increased Oxidative Stress Fluid retention and endothelial dysfunction have been related to use of nonsteroidal anti-inflammatory drugs (NSAIDs), and type 2 diabetes mellitus	Oxidative stress accelerates the development of atherosclerosis, increases inflammation, and promotes clot formation, all of which contribute to the risk of heart disease.
Antihypertensive drugs(Hydrochlorothiazide, Enalapril, Lisinopril, Ramipril)	Hyperuricemia Increased Blood Pressure	Elevate uric acid levels, which may lead to gout. It has been associated as it can cause endothelial dysfunction and contribute to inflammation in blood vessels, further raising the risk of CHD. Increase in cholesterol level, decreases the Chances of HD	Increased LDL Cholesterol and Triglycerides (Moderate to High) Hypokalemia (Moderate), It affects the heart or blood vessels congenital heart defects and peripheral artery disease. “CVD” is used based on t

Fig. 3: Mechanism of Action of *Rumex dentatus* Bioactivities

Testosterone replacement therapy (TRT)

Some studies suggest TRT may increase cardiovascular events, particularly in older men. Other studies propose TRT may improve cardiovascular outcomes in hypogonadal men (Dookun *et al.* 2022).

NSAIDs and CHD risk

COX-2 inhibitors like Celecoxib were initially thought to pose a higher cardiovascular risk. Recent reports suggest Celecoxib may not be worse than traditional NSAIDs like Ibuprofen and Diclofenac in terms of CHD risk (Dookun *et al.* 2022).

Hormonal therapy

Women suffer increased CHD risk with estrogen progestin therapy. Suggests the risk is age-dependent, with lower risks in younger postmenopausal women.

SGLT2 inhibitors

In non-diabetic populations, SGLT2 inhibitors have been shown to reduce CHD risk in diabetic patients. Ongoing studies are assessing potential benefits in non-diabetic populations. These debates highlight the complexity of CHD risk factors and the need for ongoing research to clarify the relationships between these factors and cardiovascular disease (Bonora *et al.* 2019).

Antipsychotics

The trend of antipsychotic use during pregnancy has become a notable concern for the past 10 years. Research does not provide strong evidence that antipsychotics contribute to the development of heart defects, except risperidone (Karmazyn *et al.* 2011). Recent findings show that using atypical antipsychotics i.e. risperidone subtly triggers cardiac malformation, which was noticed three months post birth, but the risk observed might not be reliable because of no known scientific or biological reason (Stanton 2003). If its use causes risk, it seems to be minor (Stanton 2003). The mentioned teratogen is not approved officially to be practiced during pregnancy. Yet they continue to be recommended when necessary and is not always needed to discontinue.

The primary functional organ to be developed in the fetus within the 42 days of beginning of pregnancy is the heart. Throughout this period, special blood vessels evolve, which eventually form the heart. By the crucial period of the second to seventh week of gestation, any disruptions in

development during these weeks might be the period when teratogen leads to congenital abnormalities. Results noticed might have occurred randomly rather than the drug itself. So as to understand the possible dangers of practicing risperidone, it demands future research (Ma *et al.* 2017).

Valproic acid (VPA)

Sodium valproate has been used for over decades for seizure control use. In relation to its benefits, it is linked with its drawbacks by inducing teratogenic risk i.e. neural tube defects and cardiac malformations. In contrast to other antiepileptic drugs such as lamotrigine and levetiracetam, VPA posed the highest risk of congenital malformations (Fischler *et al.* 2012; Ornoy 2009). The exact mechanism by which VPA causes teratogenic effects remains unclear. However, it is believed to act as a Histone Deacetylase (HDAC) inhibitor, affecting transcription factors such as Myocyte Enhancing Factor 2C (Mef2c) (Gurvich *et al.* 2005; Tung and Winn 2011). To investigate its impact on heart development, pregnant mice were treated with VPA, and ultrasound analysis revealed structural abnormalities and changes in cardiac contractility. The study suggests that Mef2c expression is not the primary cause of heart defects in mice. Instead, VPA appears to influence cardiogenesis by altering the activity of specific proteins in cells without directly modifying the genes that regulate them. This interference in how cells interpret and utilize genetic instructions may contribute to developmental issues in the fetus. In contrast to other common antiepileptic drugs, the risk of birth defects is 2–7 times higher with VPA (Ornoy 2009; Fischler *et al.* 2012). Therefore, VPA should not be the first treatment choice unless it is the only option available.

Phenytoin

Phenytoin is a known teratogen that has been linked to various birth defects due to its impact on embryonic development (Danielsson *et al.* 1997; Hansen *et al.* 2021). The possible mechanisms behind these defects include disturbances in folate metabolism, embryonic hypoxia, free radical damage from re-oxygenation, and maternal hyperglycemia (Danielsson *et al.* 1997).

Research using high-frequency ultrasound has shown that phenytoin significantly reduces embryonic heart rate, with some embryos failing to recover even after a 24 h period. These findings suggest that phenytoin-induced malformations result from a combination of embryonic and maternal bradycardia along with hyperglycemia rather than hypoxia alone (Hansen *et al.* 2021). Studies on pregnant Sprague-Dawley rats have demonstrated that the embryonic heart rate (HER) naturally increases with gestational age in control embryos. However, exposure to phenytoin significantly reduces HER, particularly within 4-8 h after dosing, likely due to its ability to cross the placenta. This suggests that phenytoin can directly cause embryonic bradycardia at specific concentrations, leading to adverse developmental effects (Danielsson *et al.* 1997). Further research on mouse and rat embryos cultured with varying concentrations of phenytoin has revealed a dose-dependent decrease in heart rate across all mouse strains, while higher doses in rat embryos resulted in arrhythmias. These observations indicate that phenytoin-induced teratogenic effects are closely linked to embryonic hypoxia caused by impaired heart function (Danielsson *et al.* 1997).

The risks associated with phenytoin are particularly concerning for pregnant women with epilepsy, as they require antiepileptic drugs (AEDs) during pregnancy to maintain seizure control. However, both monotherapy and polytherapy with AEDs have been shown to double or even triple the risk of major birth defects (Hansen *et al.* 2021). Additionally, certain AEDs may also impact cognitive development later in life, further complicating their use during pregnancy. Interestingly, class III antiarrhythmic drugs, such as almokalant, dofetilide, and ibutilide have been found to cause similar teratogenic effects as phenytoin. Like phenytoin, these drugs block the I(Kr) potassium channel and have been shown in animal studies to be highly sensitive to the embryonic heart. Their effects lead to developmental defects by causing bradycardia, arrhythmia, and cardiac arrest, which in turn result in hypoxia, oxidative stress, and altered blood flow (Bénazet *et al.* 2001; Ma *et al.* 2017).

Angiotensin-converting enzyme (ACE) inhibitors

The renin-angiotensin system helps control blood pressure. Medications like ACE inhibitors lower blood pressure by blocking the production or action of angiotensin II. However, using ACE inhibitors during pregnancy can harm the baby, causing congenital heart diseases, kidney problems, low amniotic fluid, lung issues, and poor skull development. These risks are highest in the second and third trimesters. The effects in the first trimester are less clear and may be due to reduced blood flow to the fetus rather than direct harm. Therefore, these medications should not be used during pregnancy, and women who could become pregnant should consider other options (Ma *et al.* 2017).

Drug-induced CHDs

Lisinopril: It is a medication that helps lower blood pressure and treat heart problems. However, it can be harmful to a baby if taken during pregnancy. Taking this drug in the first three months of pregnancy can increase the risk of serious birth defects, especially in the baby's heart and brain. Because of this, it is best to avoid using it during early pregnancy (Lee *et al.* 2016). The harmful effects, also known as teratogenic effects, happen due to several reasons. First, these drugs interfere with the renin-angiotensin system, which is important for regulating blood pressure and fluid balance. Second, they reduce the blood flow from the uterus to the placenta, which means the baby may not get enough

oxygen and nutrients. Third, they can directly affect the growth of heart muscle cells in the baby. Lastly, these drugs can increase the chances of the baby having low blood pressure (hypotension) and reduced blood supply to tissues (ischemia), which can affect proper development (Walters *et al*. 2012).

Captopril: It is a type of medication called an ACE inhibitor, can lead to heart problems and other birth defects in babies if taken during pregnancy, especially in the second and third trimesters. Captopril can cause birth defects if taken during pregnancy, and it works in a way similar to other ACE inhibitors like lisinopril. It can lead to problems in the baby's heart development. Some of the common issues include a hole between the lower heart chambers (ventricular septal defect), and a condition where a blood vessel that should close after birth stays open (called patent ductus arteriosus)(Crisafulli *et al.* 2020).

Captopril can also cause a hole between the upper heart chambers (atrial septal defect) and a serious condition where the left side of the heart does not grow properly (hypoplastic left heart syndrome) (Crisafulli *et al.* 2020). Because of these risks, it is very important not to use captopril during pregnancy. Women who can get pregnant should use birth control while taking lisinopril and captopril. If they want to become pregnant or find out they are pregnant, they should stop taking lisinopril and switch to a safer blood pressure medication. At around 18 weeks of pregnancy, doctors may recommend an ultrasound and heart check for the baby. Using lisinopril and captopril later in pregnancy can also cause serious problems for the baby (Lancellotti *et al.* 2023). So, it is important for women on lisinopril to talk to their doctor before planning a pregnancy or as soon as they know they are pregnant. To help prevent harm to the baby, several important steps are recommended before and during pregnancy. The women should receive preconception counseling to understand the risks of certain medications and plan safely for pregnancy (Crisafulli *et al.* 2020). A review of all current medications is important, and harmful drugs should be replaced with safer alternatives. For women at high risk, regular pregnancy testing is advised to catch pregnancy early. Early monitoring can help detect any problems in the baby's development as soon as possible. Taking folic acid supplements is also encouraged, as it supports healthy growth of the baby and helps prevent birth defects. Lastly, involving a pregnancy specialist, such as an obstetrician or maternal-fetal medicine doctor, ensures proper care and guidance throughout the pregnancy(Nakamura *et al.* 2022).

Isotretinoin: It is a powerful medication primarily prescribed for severe, treatment-resistant acne. A derivative of Vitamin A works by reducing the activity of sebaceous glands and enhancing the turnover of skin cells. Isotretinoin is a known teratogen, meaning it has the potential to cause birth defects, including CHDs, if taken during pregnancy. The highest risk of teratogenic effects occurs when the drug is used during the first trimester, which is a critical stage for fetal development (Nakamura *et al.* 2022).

Research indicates a notable increase in the incidence of CHDs in infants whose mothers used isotretinoin during pregnancy. Types of CHDs commonly linked to isotretinoin exposure include conotruncal defects, aortic arch artery malformations including transposition of great vessels, double outlet right ventricle, ventricular and atrial septal defects (VSD and ASD) as well as tetralogy of Fallot (Lammer *et al.* 1985; Mark *et al.* 2006). RA treatment induces a broad spectrum of cardiac malformations, ranging from structurally intact hearts with a normal subaortic outflow tract to severe anomalies such as a double outlet right ventricle with a straddling tricuspid orifice or a double inlet left ventricle. A notable finding within this continuum is the strong correlation between inflow and outflow tract defects, which can be attributed to disruptions in the cardiac looping process. This disturbance appears to cause misalignment of septal structures (Tarquini *et al.* 2011). According to a case report by Mondal (2017), a child was born with congenital heart defect, his echocardiography identified congenital cyanotic heart disease, including dextro-transposition of the great arteries, a 4 mm atrial septal defect, and a left-to-right shunt, with normal biventricular function. It was found that the mother had been taking isotretinoin capsule 20 mg/kg/day to treat acne recommended by a dermatologist (Tarquini *et al.* 2011; Hölscher *et al.* 2016). The child was also reported to have many other isotretinoin induced malformations. RA can disrupt the normal development of the heart, affecting the formation of heart chambers and the proper separation of the chambers, which can result in defects such as ASD and VSD, along with other malformations in major blood vessels (Hölscher *et al.* 2016).

PATHOPHYSIOLOGY OF TERATOGENIC ACTION OF ISOTRETINOIN

A major mechanism underlying isotretinoin-induced teratogenesis may be its detrimental effect on cephalic neural-crest cell activity. This disruption plays a critical role in embryonic development, potentially leading to severe congenital anomalies. Notably, interference with these cells has been linked to craniofacial deformities, CHDs, and abnormalities in thymic development(Ma *et al.* 2020). Understanding this mechanism provides valuable insights into the risks associated with isotretinoin exposure during pregnancy. Isotretinoin is a potent teratogen known to disrupt neural crest cell development, leading to severe congenital anomalies. Research indicates that both isotretinoin and its metabolite, 4-oxo-isotretinoin, interfere with cytosolic calcium homeostasis in neural crest cells, triggering cellular stress responses (Ferri *et al.* 2013). This disruption results in membrane blebbing, a characteristic feature of apoptosis, ultimately causing cell death. The loss or dysfunction of neural crest cells during early embryogenesis is a key factor

in the teratogenic effects of isotretinoin. Understanding this mechanism provides valuable insights into the risks associated with isotretinoin exposure during pregnancy. Underscoring the critical need for strict precautions when prescribing it during pregnancy and importance of strict regulatory measures to prevent fetal harm (Varricchi *et al.* 2018).

According to the research of Bouman (1995) on chicken hearts after administering RA treatment he observed VSD and DORV showing dextraposed arterial pole and many other abnormalities. He concluded that RA treatment in chickens induces a broad spectrum of cardiac malformations. A notable finding within this continuum is the strong correlation between inflow and outflow tract defects, which can be attributed to disruptions in the cardiac looping process (Varricchi *et al.* 2018). These insights highlight the critical role of cardiac looping in proper heart development and the potential teratogenic effects of RA exposure. RA influences heart tissue specification, structural patterning, and neural crest development. While its deficiency can disrupt heart formation, excessive RA exposure has been linked to congenital defects in animal models. The active form of isotretinoin, RA, interferes with normal fetal development by affecting processes like cell differentiation, programmed cell death (apoptosis), and blood vessel formation (angiogenesis) (Iqubal *et al.* 2018).

RETINOID IMPACT ON GENE REGULATION

Isotretinoin works by binding to nuclear RA receptors (RARs and RXRs), which regulate the expression of specific genes involved in cellular differentiation, tissue maintenance and embryonic development. RA influences genes responsible for heart formation by regulating transcription factors involved in cardiogenesis. Disruption of these factors can lead to abnormalities in the folding, septation, and overall formation of the fetal heart (Iqubal *et al.* 2018). RA balance is very important for embryo development at every stage. RA levels are precisely regulated through a complex interplay between synthesizing and metabolizing enzymes. Retinoids bind to RA and retinoid X receptors (RARs and RXRs), initiating a regulatory cascade that governs the expression of tissue-specific genes. Genetic or nutritional disruptions in RA signaling may serve as a significant risk factor, contributing to an increased prevalence of congenital heart diseases in humans(Florescu *et al.* 2013). According to Liu (2018), isotretinoin exposure disrupts mesodermal differentiation by altering gene expression and chromatin accessibility. RNA-seq analysis reveals dysregulation of key signaling pathways, such as TGF-beta, while ATAC-seq indicates increased DNA binding of transcription factors like HNF1B, SOX10, and NFIC near affected genes. These findings suggest potential molecular mechanisms through which isotretinoin interferes with mesodermal differentiation, impacting cardiac development(Varga *et al.* 2015).

CHD-DRUGS PREVENTION STRATEGIES

Research suggests that isotretinoin therapy at a dosage of 0.8 mg/kg/day poses no significant risk of polymorphic ventricular tachycardia, making it a safe option for acne treatment. This dosage appears to maintain cardiac safety while effectively addressing dermatological concerns, reinforcing its suitability for clinical use. To prevent the isotretinoin induced CHD and other abnormalities, pregnancy prevention programs (PPPs) should be implemented worldwide (Varga *et al.* 2015). It is seen that in those countries where there are no PPP's, it is estimated that around 80% of pregnant women come into contact with isotretinoin either within the advised 30-day contraception period or while they are pregnant. Studies indicate that women who continue taking isotretinoin beyond the 15th day after conception face a 35% risk of their offspring developing isotretinoin embryopathy and 40% risk of abortion and stillbirth. Pregnancy during isotretinoin treatment indicates a failure of preventive measures. To minimize risk, two forms of contraception should be used starting one month before treatment begins and continuing until one month after discontinuation (Varga *et al*. 2015).

CONCLUSIONS

CHDs basically affect about 1% of live births worldwide, which makes it one of the pervasive birth defects. Either these defects may be minor or might need surgery for its cure. There are certain types of drugs discussed above that can cause birth defects within the babies. The drug classes that lead to birth defects are described above. Normal heart formation is affected when following mechanisms take place by taking the specific type of drug, oxidative stress, apoptosis, folate metabolism disruption, interference with cardiac signaling pathways, altered hemodynamics etc. Moving towards the classes of the drugs that lead to CHDs, these drugs which show the risk of the CHDs are needed to be replaced with the drugs that have less risk factor of CHDs. Considering anti-psychotics, all their types somehow show CHDs risk except for the drug risperidone as it shows the risk but it is not as the other drugs, rather it is one of the minor risks which can be treated. During pregnancy it is mentioned for the patient only if necessary.

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AUTHOR CONTRIBUTIONS

All authors made equal contributions to the conception, design, execution, and writing of this study.

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RESEARCH ARTICLE

Prophet's Legacy and Women's Dignity in Islam: Exploring Concepts of Equality and Justice in Islam and Addressing Violence Against Women

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ABSTRACT

Background: The life of Prophet Muhammad (PBUH) is central in understanding equality and justice in Islam. It has deep notions regarding the rights of women. It reflects the significance of Islam in upholding the dignity of all persons, particularly women.
Objectives: This study aims at reintroducing Islamic principles into contemporary discussions of gender equality in Muslim-majorities. This study highlights how the Islamic context and teachings play a key role in addressing violence against women.
Methodology: A multi-method research strategy was employed to study the ethical and historical dimensions of the *Seerah.* This qualitative study seeks to determine how cultural practices influence Islamic teachings regarding gender equality in societies in which Muslims constitute majority of the population.
Results: Islamic theology reminds the value of justice and equality. Through careful analysis of the primary Islamic context and its interpretations, this article demonstrates that Islam elevated women's status from the degraded position they held in pre-Islamic societies to one of dignity and respect. While cultural practices in some Muslim majority regions have sometimes diverged from these teachings, however, foundational Islamic texts and Seerah themselves offer a framework of gender justice, equity, and women's empowerment.
Conclusion: There is a need to judge historical accounts in the context of the times they were written and sift them to discover solutions to contemporary social problems. Moreover, it is important to restate these fundamental principles to safeguard women's dignity and their rights for a safe and equitable life.

INTRODUCTION

Investigation of the relationship between human rights, women's dignity, and Islam's *Seerah* is a fundamental necessity to resolve the current violence against Muslim women. Critical analysis of historical contexts, Islamic ideology, and current problems provides a framework for upholding the dignity and respect for women. The *Seerah*, which chronicles the life and teachings of the Prophet Muhammad (PBUH), provides in-depth knowledge of social justice and gender equality principles of Islam. It enables mankind to relate the *Seerah's* central values to gender equality and human rights. Prior to Islam, repressive patriarchal norms brutally restricted women in pre-Islamic Arabian society (Ćustović 2025). Female infanticide was among the notorious practices of this period, when women were treated as little better than property. However, with the advent of Islam in the 7th century CE, society changed dramatically. The Quran explicitly writes, "*and for women are rights over men similar to those of men over women*" (Quran 2: 228). This strong verse forms the foundation of gender equality, which is strongly evident in the teachings and practices of Prophet Muhammad (PBUH). He uttered in his final sermon, "*O people! It is true that you have certain rights over your women, but they also have rights over you*" (Sahih Al-Bukhari 6130). Scholarly explanations of the *Seerah* elucidate the Prophet's liberal position on women's rights. As noted by influential feminist scholar Fatima Mernissi, "Islam did not come to oppress women; it came to liberate them from oppressive traditions" (Mernissi 1991).

Her observations lead us to interpret the teachings of the Prophet (PBUH) as liberative, not restrictive. She urged that all must see how the *Seerah* contributes to modern gender inequity, particularly in Muslim societies where culture tends to override Islamic scriptural teachings. While women's equality is clearly articulated in Islamic scripture, however, there are gaps between the implementation of these principles in many Muslim-majority nations. Majority of the cultural norms, more commonly falsely described as religious mandates, fuel the continuum of violence against women.

Leila Ahmed asserts that Muslim women's violence is largely a result of "historical and cultural practices that are mistakenly interpreted as Islamic" (Ahmed 2021). The misinterpretation warps the true nature of Islam and makes normality out of violence towards women. Scholars such as Ziba Mir-Hosseini asserted that the Islamic legal framework needs to be reinterpreted and reformed at an urgent rate. Mir-Hosseini believes that "we must approach the texts in a manner that is respectful of their ethical and moral imperatives and yet can speak to contemporary realities" (Mir-Hosseini 2006). An effort must be made to reconcile the interpretation of the *Seerah* with contemporary notions of gender equality and human rights. Reinterpretation is required to counter the root causes of violence against women, including harmful cultural practices and poor legal safeguards (Orr 2020).

Most Islamic cultures are still unable to incorporate equality and justice into their core values despite the advancements made by women's rights in Western legal systems. The US Violence Against Women Act is an example of a commitment to preventing domestic abuse and violence against women. Sadly, most Muslim-majority states fail to protect women's rights because of patriarchal interpretations of Islamic law. As Kecia Ali asserts, women's rights in Islam and advocating for legislative reforms consonant with the Quran and modern human rights principles necessitate a feminist interpretative approach to Islamic texts (Ali 2024).

In addition, gender and violence sensitivity in culture have increasingly come to matter in international human rights forums. The Universal Declaration of Human Rights declares that everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind. Yet the implementation of these ideas is frequently at odds with native customs and religious beliefs. It is difficult to balance promoting universal women's rights and respecting cultural traditions. This equilibrium is particularly important in Muslim societies, wherein the *Seerah* may be a potent historical basis for advocating women's rights and dignity (Assembly 1948; Forouzanfar *et al*. 2016). Islam's intricate tapestry of religious, cultural, and historical factors is echoed in the dynamic interplay between the *Seerah*, human rights, and women's dignity (Nasir 2020). The *Seerah* and Quranic teachings emphasize women's dignity, protection from harm, and providing justice, but the gap between these principles and current social practices in Muslim majority societies is significant.

The S*eerah's* fundamental concepts regarding social justice and equality has much potency to assist in resolving the immediate issue of violence against women today. This study reintroduced Islamic principles into contemporary discussions of gender equality in Muslim majorities, and highlights how women's dignity and rights are respected by the teachings of the Prophet Muhammad (PBUH) and promotes a new understanding of Islamic scriptures.

MATERIALS AND METHODS

This qualitative study seeks to determine how cultural practices influence Islamic teachings regarding gender equality in societies in which Muslims constitute the majority of the population. It highlights the contrasts between Islamic teaching and social custom in a literature review and scholarly analysis. For this purpose, Amnesty International and UN Women reports and feminist accounts by scholars Tariq Ramadan, Fatima Mernissi, and Leila Ahmed were used as the primary sources of information, while first-hand data were collected using semi-structured interviews of activists, legal professionals, and Islamic feminists. It also discussed historical documents and present-day legal frameworks. This research also acknowledged potential biases, limited generalizability, and difficulty in gaining diversified views in conservative settings. This research proposed to clarify the complex interrelation between cultural norms and Islamic principles, offering pragmatic solutions for enhancing gender equity based on the Quran and the Seerah (Koburtay *et al.* 2007).

RESULTS AND DISCUSSION

This research demonstrates a complex interrelation among cultural norms, Islamic doctrine concerning gender justice, and the dreadful reality of gender violence in Muslim society. While the dignity and safety of women are prioritized in the Quranic message and the Seerah, most Muslim societies continue to present a stark contrast between these ideals and current social mores. Islamic feminism is an immense force against patriarchal interpretations and retrieving the gender-equitable principles within the Quran and the Seerah. Scholars argue that Islamic history has been influenced by centuries of male-centric interpretations, and Islam is not patriarchal. This perspective challenges traditional paradigms and demands a reassessment of Islamic law that does not overlook the historical and contextual circumstances. Islamic feminist approaches showed that contemporary gender relations must be patterned considering Seerah. The verses in the Holy Quran that identify with equality and justice are often excluded in support of interpretations that promote male hegemony. Women's rights have nevertheless been undermined by historically patriarchal approaches of Islamic law; however, gender-based violence has been aggravated by the misuse of Islamic scriptures (Bakar and Sahman 2024).

The present study highlights the role of cultural norms in perpetuating violence against women, particularly in countries like Pakistan, Afghanistan, and Egypt. Honour-based values often clash with Islamic principles that prioritize women's dignity and autonomy. For example, honour killings in Pakistan, Afghanistan, and Egypt are justified as protecting family honour, which contradicts the Quran and *Seerah*. The verse (4:34) shows clearly that the privileged position of men over women is a condition related to the support of women. However, some men tend to hold the view that the influence of men over women is unconditional because women are inferior to them and possess a lesser position than men (in reason of strength). This interpretation does not hold a strong position as the verse (4:34) does not mention or imply that the privileged position of men is purely materialistic. Intersectional influences like socioeconomic status, ethnicity, and geographical location play a major role in determining violence against Muslim women. Despite this, in Muslim countries, many women suffer from restrictions and physical and mental abuse. Furthermore, the challenges that women face differ from one country to another because each country laws and governments are not the same. In rural communities, poverty and lack of access to legal services, women more likely to become victims of violence and face limited access to justice. Failure to implement existing legislation further fuels violence. The enforcement agencies do not take violence against women seriously in the light of entrenched cultural biases. This is more common in societies where women experience cultural stigma and social impediments in reporting violence. Scholars have highlighted the need for social reforms aimed at strengthening legal mechanisms and initiating gender sensitive training of security personnel and the judiciary laws (Mojahed *et al.* 2022; Baryar 2023). In cultures where honour is an important value, men will be the honour providers. Therefore, if family honour has been lost due to a female member of the family, there will be a desire for instant action for the retrieval of the family honour. In most of nations in the world, women are killed to save the family honour. However, Islamic concepts of equality and dignity for women are mismatched with honour-based killings (Yousaf *et al.* 2025). This is one part of our patriarchal culture that views women's bodies as repositories of honour or as men's property. Religion and culture, then, just become tools to maintain these roles and to enforce compliance. Law, then, must play a larger role in protecting women from honour killings (Huda *et al*. 2025).

This study highlights the need to empower women against violence and suggests the incorporation of Islamic scholarship on women's rights, legal reform, and education. Moreover, it demands the prohibition of gender-sensitive interpretation of *Seerah* and Quranic ideals. This would lead to the creation of new models of legislation that depict the actual context of Islamic ideology and promote justice and equity of Muslim women. Community action should also be undertaken to eradicate cultural factors leading to violence against women. Educational campaigns on the values of compassion, justice, and dignity, as interpreted from *Seerah*, can also effectively curb gender-based violence. Islamic scholars and leaders should take the initiative to create interpretations of the Islamic context that are non-violent and positive of women's rights.

CONCLUSIONS

The present study shows Islamic values can transform gender justice by prioritizing the context of *Seerah*, human rights, and women's dignity in Islam. Islam has faith in gender equality and respect, but these are generally replaced with patriarchal ideology and cultural practices. Islam does not allow violence against women in the name of family honour. The practice of justice and mercy of the Prophet (PBUH) is in contrast to honour killings and forced marriage. Radical legislative change and religious scholar backing are required to realize gender justice. For the awareness of equity and to empower Muslim women, the training of society, legal and police personnel is required urgently. This sensitive analysis shows that the true teachings of Islam represent a high-level framework of rights, equality, and protections, when applied in apt ways, can provide women's dignity and empower them to participate fully in religious, family, economic, and social life. Effort to reform and implement these teachings is one of the major needs in Muslim-based culture.

AUTHOR CONTRIBUTIONS

AQG and ZH wrote and reviewed and approved final draft.

CONFLICTS OF INTEREST

The authors affirm that they possess no conflicts of interest.

DATA AVAILABILITY

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REVIEW ARTICLE

Toothed Dock (*Rumex dentatus*) – Deciphering its Medicinal Realm

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ABSTRACT

Background: toothed dock (*Rumex dentatus* L) has been extensively utilized in traditional medicine across the world for treating various diseases. Different parts of the plants have been used for centuries in the treatment of a wide range of diseases.
Objective: This study evaluates the current level of knowledge regarding the pharmacology, phytochemistry, ethnopharmacology, and toxicity of toothed dock. This review has compiled and examined all of the compelling evidence regarding its traditional uses that has been backed by pharmacological research to determine its applicability as a possible medicinal plant.
Methodology: This review highlights current scientific findings related to its phytochemical constituents and therapeutic properties. Literature was collected primarily through Google Scholar, with access to articles from PubMed, Science Direct, and Research Gate. Most studies reviewed involved phytochemical screening and biological assays. These effects have been demonstrated through various i*n vitro* and *in vivo* studies.
Results: Toothed dock demonstrates significant antibacterial activity against multidrug-resistant pathogens. It reduces the expression of inflammatory markers. The plant shows quite strong scavenging abilities towards free radicals and reduces blood glucose levels. Key bioactive compounds include flavonoids, anthraquinones, phenolic acids, and tannins.
Conclusion: It has ethnomedicinal, antibacterial, antioxidant, anti-inflammatory, antidiabetic, anticancer, and allelopathic properties. Despite promising therapeutic potential, significant research gaps exist in clinical validation and safety assessments. This review provides a foundation for evidence-based utilization of the toothed dock in modern healthcare.

INTRODUCTION

Since ancient times, people have been utilizing plants for therapeutic purposes. Egypt, China, and India all use these plants for a variety of medicinal purposes (Zhou *et al*. 2020; Asigbaase *et al*. 2023). Most people believe that natural remedies are not only readily available but also reasonably priced. Additionally, they typically have no adverse side effects (Shikov *et al*. 2021). Herbal remedies are two to three times as popular worldwide as prescription medications. Most of modern medicine is based on the ancient use of plants for medical treatment, which existed before the written records of humanity. Polygonaceae family is important due to its pharmaceutical properties. The knotweed or smartweed families are other names for the Polygonaceae family (Chaudhury *et al*. 2021). Because of its ecological and therapeutic significance, botanists are particularly interested in the genus *Rumex*, which includes species like toothed dock here are approximately 200 species that belong to this genus, and some possess beneficial pharmacologic properties (Li *et al*. 2022).

It is an herbaceous perennial plant with a variety of morphological traits. They have deeply toothed or serrated edges and are ovate to lanceolate in shape. This is the reason behind the common name for this plant (Munir *et al*. 2016). Toothed dock has thrived in many parts of the world, particularly the temperate and subtropical zones. Because of its quick growth and ability to displace native vegetation, it

may be considered an invasive species in some regions of the world. It is considered a weed in the majority of regions, particularly in places where it has become naturalized (Jamil *et al.* 2025). Due to the wide range of biological uses of plants and compounds derived from them, toothed dock was selected for characterization of phytochemicals, medication, conventional benefits, and allelopathic properties. This review evaluates the current level of knowledge regarding the pharmacology, phytochemistry, ethnopharmacology, and toxicity of toothed dock. This review has compiled and examined all the compelling evidence regarding its traditional uses that has been backed by pharmacological research to determine its applicability as a possible medicinal plant.

PHYTOCHEMISTRY

Phytochemicals are plant-based compounds that have therapeutic and health benefits, such as preventing and curing illnesses. Foods naturally contain them, and work in association to treat various infections. Researchers from all over the world studied toothed dock, extracted several phytochemicals, and conducted various biological tests for numerous bioactivities (Khaliq *et al.* 2023a). According to preliminary phytochemical analyses, toothed dock contains alkaloids, tannins, terpenoids, quinones, flavonoids, cardiac glycosides, and saponins. There are now sixty three compounds that have been identified and isolated. Quinones, chromones, naphthalene glucoside, c-glucosyl anthrones, flavonoids, stilbenes, and essential oils are also phytochemical constituents of toothed dock (Khalil *et al.* 2022; Fig. 1).

MEDICINAL PROPERTIES

It has medicinal properties and is used to treat many diseases (Beshah *et al.* 2020), such as anti-inflammatory, stringent, tumor-fighting, diuretic, and antidermatitic. Additionally, it contains cholagogues, laxative agents, and has a tonic nature. According to observations, every part of the toothed dock has significant and practical medical uses. Conventional uses of the plant's leaves included diuretic, refrigerant, and cooling properties. Toothed dock roots were utilized as a purgative, dysentery, and anti-ascariasis remedy. Traditionally, the plant has also been utilized to heal a number of infections caused by bacteria and fungi, such as dysentery, ascariasis, and enteritis (Thaher *et al.* 2024). Fig. 2 shows the most common traditional uses of this plant and its modern scientific validations (Khaliq *et al.* 2023a).

Toothed dock has been used in folk medicine, especially in different cultural regions of Asia and Europe. Diverse therapeutic applications ranging from anti-inflammatory, antimicrobial, antioxidant agents, cytotoxic, antibacterial, antifungal, hepato-protective, antitumor, and skin disorders. It included flavonoids, tannins, and phenolic acids. Methanol, hexane, ethyl acetate, chloroform, DCM

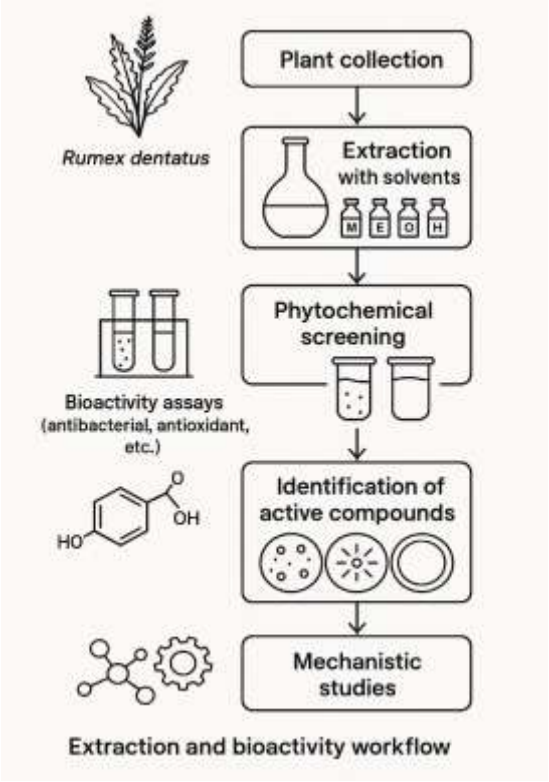

Fig.1: Overview of extractions and bioactivity workflow

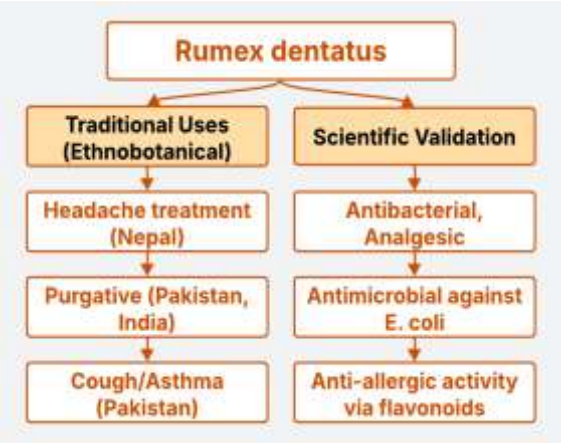

Fig. 2: Traditional uses and scientific validation of *R. dentatus*

(dichloromethane), and H_2O are among the diverse solvents tested for a range of biological assays. Notably, extracts from various parts, such as the leaves, stem, and roots, demonstrated primarily distinct biological assays. Previous research also demonstrated that the methanolic extracts of shoots and roots were active against every bacterial strain examined. However, the hexane extract was more effective than the methanolic extract for inhibiting fungal growth (up to 80%) (Khaliq *et al.* 2023a). Toothed dock shoots have been utilized as an astringent to treat skin conditions and produce purgative outcomes. Leaves and shoots were utilized as

cooling agents, diuretics and refrigerants. Disorders relating to bones and pain were known to be significantly cured by using this plant. As a result, the plant was used to relieve body pain and apply a potent decoction to dislocated bones. Asthma, coughing, jaundice, high temperature, fragility, scabies, foot, mouth illness, and other ailments were also treated with its roots and leaves. In India, this plant is used in a diverse array of traditional consumptions. Therefore, it was considered extremely important (Lal *et al*. 2024).

ANTIMICROBIAL PROPERTIES

One of the most important scientific concerns of our day is the global issue of antibiotic resistance. The development of novel antibiotics is an exhausting and lengthy process. Several bioactive components found in this plant can be utilized for treating infections and multidrug-resistant bacteria. Aqueous and methanolic extracts showed significant antibacterial activity against various strains. Its water-based extracts are particularly effective against *Pseudomonas aeruginosa*. Its phytochemical screening confirmed the presence of terpenoids, carbohydrates, and phenolics (Zakir *et al*. 2020). Najafabadi *et al*. (2020) assessed the impact of different methanolic extract concentrations on *P. aeruginosa* biofilm formation for 48 and 72 hours. Due to the bacteria's ability to withstand antibiotic treatment, *P. aeruginosa* biofilm formation accounted for a significant percentage of hospital-acquired infections. *P. aeruginosa* biofilm's extracellular polymeric material was a mixture of extracellular proteins, polysaccharides and microbial cells. To cultivate biofilm and assess the antibiofilm action, they employed the microtiter plate method. Gas chromatography was used to examine the arrangement of the methanol sample. Methanolic extracts also inhibited *P. aeruginosa* biofilm formation in a dose-dependent manner, with a minimum biofilm inhibitory concentration (MBIC) of 250 mg/mL.

Using the extract of its leaves, Rehan *et al*. (2020), isolated its phytochemical compounds to test for antibacterial activities. They extracted hexacosanol and hexacosanoic acid by using spectroscopic analysis. Molecular analysis was used to determine the antibacterial relationships of isolated compounds. Using the agar well diffusion assay, the antibacterial behaviour against various bacterial strains was assessed. *Staphylococcus aureus* showed maximum inhibition due to its phytochemicals, indicating strong antibacterial activity. The extract and hexacosanol compound showed the best effects on *Escherichia coli* (20 mm) and *S. aureus* (23 mm). Khan and Ahmed, (2022) also assessed the antimicrobial properties by using different solvents. Specifically, water, ethanol, ethyl acetate, methanol, and hexane extracts were tested. Using the *in-vitro* agar diffusion technique its antimicrobial activity was confirmed against Gram-positive bacteria such as *Bacillus atrophoeus*, *S. aureus*, and *Bacillus subtilis*; Gram-negative bacteria such as *Klebsiella pneumoniae*, *E. coli*, and *Salmonella typhi*; and fungal strains such as *Rhizopus stolonifer*, *Candida albicans*, and *Aspergillus niger*. The order of effectiveness of the various solvent extracts ethanol> ethyl acetate> methanol> hexane> aqueous extracts. It showed a zone of inhibition of 22±0.23 mm. The plant ethanolic extract under study demonstrated the highest inhibitory activity against the fungus *C. albicans*. Ethanolic extract also demonstrated a significant effect against all bacterial strains. It showed a zone of inhibition of 18±0.16 mm for S. aureus and 19±0.08 mm for *E. coli*. Whole plant extracts contain bioactive substances with strong antibacterial and antifungal properties. Additionally, based on the many strains of organisms the zone of inhibition order was fungi> Gram-positive bacteria> Gram-negative bacteria.

For *in vitro* analysis, the disc diffusion method and brine shrimp mortality assay were performed by Moniruzzaman *et al*. (2023). These in-silico studies were conducted using standard computational tools and servers, including Discovery Studio, PyRx and Pymol. *S. aureus* was collected from eczema patients' infected areas and identified using 16S rRNA analysis, biochemical analysis, and morphological analysis. Leaf methanolic extract demonstrated the maximum region of resistance (14.33 ± 0.68 mm) when applied at a dose of 150 µg/disc on *S. aureus*. Thus, the leaf extract from toothed dock could be utilized as an organic medicine source to fight the pathogen that is resistant to antibiotics.

Agar well diffusion and minimum inhibitory concentration assays on medical isolates of *P. aeruginosa* were used by Khan et al. (2024) to assess the antibacterial activity of the methanolic extract of Toothed dock root. MIC values for the crude extract, fractions and subfractions tested ranged from 200 to 1000 µg/mL, respectively. Notably, the water fraction had the strongest anti-*P. aeruginosa* activity among the fractions. A spectroscopic analysis employing HPLC-ESI-Q-TOF-MS revealed that emodin and gallic acid were the main constituents and their fractions were the same that produced the antibacterial and antibiofilm effects. This study offered strong evidence in favour of its traditional use as described in folklore. Additionally, this investigation advanced our knowledge of its ability to treat infections. According to Nazir et al. (2022), biologically synthesized ZnO nanoparticles by using its leaf extract and showed significant antibacterial activity. According to Khaliq *et al*. (2023b), toothed dock yielded five bioactive molecules. Furthermore, the majority of the plant extracts exhibited significant to mild antimicrobial action ($IC_{50,}$ half-maximal inhibitory concentration), when tested on six pathogenic organisms from humans, which included five bacteria and

one fungal pathogen. In the microtiter plate assay, the n-hexane and methanolic extracts were identified to have beneficial antibacterial ability out of all the extracts that were assessed for antimicrobial activities. Moreover, advanced phytochemical studies identified nineteen natural products, mainly anthraquinone derivatives, with most fractions showing inhibitory activity against *S. aureus* and some also active against *E. coli* and *C. albicans* (Aierken *et al*. 2023). This study identified that one of the new compounds isolated from the roots, specifically musizin that exhibited moderate antifungal activity. This compound demonstrated an inhibitory rate of 39.539 ± 0.412% against the fungus *Epidermophyton floccosum* at a concentration of 100 μM. This suggested that this plant may have potential applications in treating fungal infections, particularly through the activity of its phenolic compounds (Li *et al.* 2023). Silver nanoparticles or AgNPs were widely used in medicine because of their strong antimicrobial properties. Amir *et al*. (2023) prepared tooth dock silver NPs and tested Gram-positive *S. aureus* and Gram-negative *E. coli* bacterial strains to assess their antibacterial activity. They recorded more antimicrobial activity against *E. coli* and it was near to the usual control group. According to SEM and XRD morphological analysis, the plant extract is responsible for the agglomerated, polydispersed, spherical shape of the nanoparticles as well as their high display of inconsistent morphology.

ANTIOXIDANT PROPERTIES

Natural substances called phytochemicals exist in plants and are vital for supporting human health. Phytochemicals act as antioxidants and provide defence against harmful free radicals. This antioxidant action enhances the general health of cells (Pawase *et al*. 2024). Spectrophotometric assays were one of the specific methods used to measure the activity of antioxidant enzymes. These tests measured how quickly the enzymes react with particular substrates. Toothed dock increased activities of antioxidant enzymes (peroxidase, catalase, superoxide dismutase) when exposed to lead and zinc, helping the plant neutralize reactive oxygen species and suggesting strong adaptive antioxidant defence. It has been assessed by different studies using techniques like TPC, TFC, and DPPH for its antioxidant properties. Ethyl acetate extracts from roots and leaves showed high total phenolic content and strong DPPH radical scavenging activity (IC_{50} as low as 0.012 mg/mL). Moreover, β-carotene bleaching assays confirm potent antioxidant properties linked to phenolic compounds (Elzaawely and Tawata 2012). A study by Humeera *et al.* (2013) demonstrated that the extracts of this plant showed antioxidant activity and were helpful for neutralizing free radicals. DPPH assay, riboflavin photooxidation, deoxyribose assay, and lipid peroxidation assay were used to evaluate the antioxidant activity. This validated the accuracy of the findings. The petroleum ether extract has a lower total phenolic content (45 μg/mg). The butanol extract has the highest TPC (145 μg/mg). This variation in phenolic content affected the total antioxidant capability of the various samples. Moreover, its extracts exhibited dose-dependent scavenging of hydroxyl and superoxide radicals. Butanol extracts showed the highest total phenolic content and antioxidant capacity with the presence of tannins, terpenoids, and flavonoids (Humeera *et al*. 2013). Polar lipid fractions were especially associated with antioxidant activity, as confirmed by advanced chromatography and mass spectrometry (Elfotoh *et al*. 2013). Methanolic extracts of shoots and roots also showed significant DPPH scavenging activity. The higher antioxidant activity was seen in aerial parts. The quantitative study of roots and shoot extracts revealed a high content of tannins and phenolics. Toothed dock extracts demonstrated scavenging activities of 52.88% for roots and 62.78% for shoots at 50 mg mL^{-1}. For roots and shoots the coastal samples had IC50 values of 23.99 and 34.99 mg mL^{-1} for methanolic extract. The coastal and inland samples had respective IC50 values of 31.67 and 41.59 mg mL^{-1} (Hafaz *et al*. 2022). Ethanol and methanol extracts demonstrated up to 96% and 85% DPPH inhibition at 300 μg/mL, comparable to ascorbic acid and butanol fractions that showed 90% inhibition in lipid peroxidation assays (Khalil et al. 2022), suggesting strong antioxidant potential.

ANTIDIABETIC ASSAY

A condition known as diabetes is brought on by an excessively high blood glucose level, or blood sugar. The primary energy source that comes from food is glucose. The pancreas produces the hormone insulin, which facilitates the uptake of glucose from food for energy production. Nepodin, isolated from toothed dock, showed significant antidiabetic effects by stimulating glucose uptake in cultured L6 myotubes through the activation of AMPK (AMP-activated protein kinase). This led to enhanced GLUT4 (glucose transporter protein 4) translocation, crucial for cellular glucose entry. In diabetic mice (C57BL/KsJ-db/db), nepodin improved glucose tolerance and reduced fasting blood sugar, confirming its mechanism via AMPK activation and GLUT4 regulation (Ha *et al*. 2014).

Toothed dock was recognized for its potential antidiabetic properties through a range of experimental studies. One of the most prominent findings was its ability to significantly reduce blood glucose levels. This indicated its role in counteracting hyperglycemia, which is a primary characteristic of diabetes. Toothed dock can enhance insulin

sensitivity. Polyphenol-rich extract significantly lowered blood glucose and improved insulin sensitivity in type 2 diabetic rats. Toothed dock also up-regulated *PPARγ* (peroxisome proliferator-activated receptor gamma) expression, a key regulator of glucose and lipid metabolism and inflammation suppression. Molecular docking showed strong binding to *PPARγ*, confirming their involvement in glucose homeostasis (Elsayed *et al*. 2020). It improved carbohydrate metabolism, reduced insulin resistance, and alleviated liver damage and hyperglycemia in diabetic rats. Gene expression and *in-silico* studies confirmed that isolated compounds from toothed dock bind to *PPARγ* and help lower blood glucose, highlighting its promise as a natural antidiabetic remedy (Khaliq *et al*. 2023a). Fig. 3 shows a flowchart of the mechanism of action of all the bioactivities mentioned above of the toothed dock.

ANTICANCER PROPERTIES

The term "cancer" describes any of a wide range of illnesses that are characterized by the unchecked and aberrant proliferation of cells that can infiltrate and destroy healthy body tissue. It is frequently possible for the illness to spread all over the body. Since cancer is the 2nd most common cause of death worldwide therefore its effective treatment is required. The study used a brine prawn cytotoxicity assay along with the potato disc experiment. Frequently employed as a first assessment for medicinal activity, this technique offers valuable information regarding the possible toxicity of herb extracts. Extracts showed weak to moderate inhibition of carcinoma cell growth *in vitro*, with higher concentrations yielding better effects. *In vivo* testing in mice (Ehrlich ascites carcinoma model) confirmed dose-dependent cytotoxicity (Hawas *et al.* 2011). Batool *et al*. (2017) assessed their anticancer activity against the cell line MDA-MB-231, which exhibited invasive characteristics. The MTT assay was utilized to assess the toxicity against a cancer cell line. To examine any alterations in the cell cycle or apoptotic effect, flow cytometry was used. The disruptive and wound-healing abilities were also investigated along with the NF-κB pathway and Western blotting of apoptotic genes. Extracts used were methanol and chloroform. Cell proliferation was mostly inhibited in both terms of concentration and time. By suppressing the stimulation of NF-κB and the resulting transcripts, surviving, Cyclin D1, XIAP, Bcl-xl and Bcl-2, it was demonstrated that both RC and RM prevented growth of cancerous cells and caused cell death. Methanolic and chloroform extracts and isolated compounds, showed cytotoxicity against lung (A549), breast (MDA-MB-468, MDA-MB-231), pancreatic (MIAPaCa) and colon (HCT-116) cancer cell lines. One compound (B) had strong activity against colon cancer cells (IC50 = 11.29 µg/mL) and inhibited cell migration and invasion (Khaliq *et al*. 2023c). Neopodin and other compounds from toothed dock roots exhibited antiproliferative and pro-apoptotic effects in various cancer cell lines, supporting their potential as natural anticancer agents. Toothed dock roots yielded compounds showed antiproliferative activity against several cancer cell lines. NMR spectroscopy was used to clarify their planar structures. However, because of differences in the precise rotation values, their exact configurations were still unknown. L-glucosides and their derivatives found in nature are special compounds with important pharmacological and biosynthetic potential. Toothed dock extract, in combination with cisplatin, enhanced anticancer effects against oral squamous cell carcinoma (HNO97) cells by promoting cell cycle arrest, apoptosis and reducing autophagy. Network pharmacology suggested involvement of EGFR, microRNAs and PI3K-Akt pathways, indicating potential for combination therapy (Ragab *et al*. 2025).

ANTI-INFLAMMATORY PROPERTIES

Tissue damage from toxins, bacteria, heat, trauma, or any other source triggers the inflammatory response, or inflammation. The dysregulation of numerous intracellular signaling pathways, such as kinases cell, surface receptors and transcription factors, is a common feature of chronic inflammation. Toothed dock contains flavonoids, tannins and phenolic acids, which are linked to its traditional anti-inflammatory uses. Analytical studies confirmed these compounds and established quality standards for herbal preparations (Singh *et al*. 2013). Ethanolic extracts of Toothed dock leaves and stems showed anti-inflammatory and antioxidant effects in rats, reducing inflammatory markers (TNF, IL-2, IL-6), improving liver and kidney function and lessening fibrosis. Leaves, with higher phenolic content, were particularly effective (Mohamed *et al*. 2014).

Toothed dock extracts reduced the expression of inflammatory markers (COX-2, TNF-α, p-NF-κB) in gastric tissues and lowered pro-inflammatory cytokines (IL-8, PGE2) in models of ethanol-induced gastric injury. Extracts also restored antioxidant enzyme levels, supporting their role in protecting against oxidative stress and inflammation (Qazi *et al*. 2022). Toothed dock has been shown to reduce the expression of inflammatory markers like COX2 and TNF-α, indicating its potential being an anti-inflammatory agent. The plant was also classified in a lower toxicity class (Kazamel *et al*. 2024).

ALLELOPATHIC PROPERTIES

The term "allelopathic properties" describes the chemical interactions that occur between plants. Plant produces

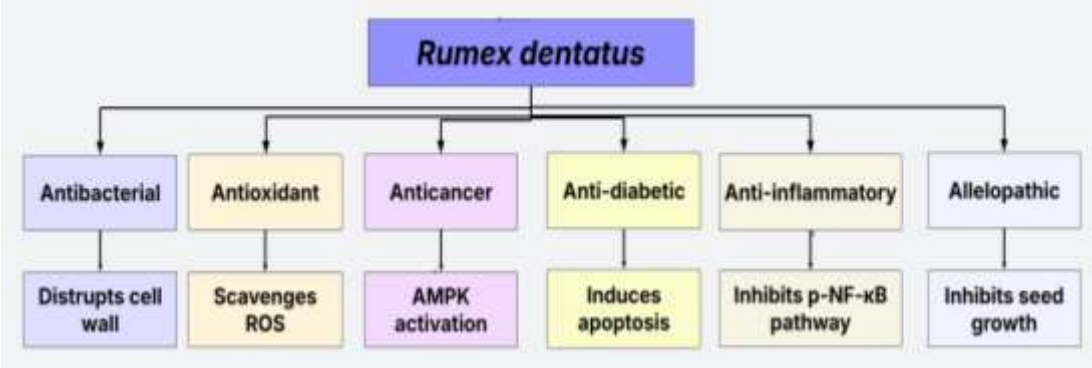

Fig. 3: Mechanism of action of *R. dentatus* bioactivities

biochemicals called "allelochemicals" that can affect the behaviour, growth, survival, or reproduction of other plants. Different studies examined the allelopathic effect of aqueous extracts of toothed dock and other plants. Root extracts of Toothed dock, rich in allelochemicals like vanillic, caffeic, benzoic, sinapic, gallic, ferulic, and cinnamic acids. Higher extract concentrations increased lipid peroxidation and hydrogen peroxide, while catalase and superoxide dismutase activities were also elevated, suggesting oxidative stress as a mode of inhibition. Cinnamic and ferulic acids were particularly effective in inducing these effects, highlighting toothed dock as a bioherbicide (El-Shora *et al.* 2014). Its aqueous extracts reduced germination, radicle, and plumule growth in both intact and pre-germinated seeds of weeds (*Avena fatua*) and crops (sunflower, maize, wheat). Filter paper and soil bioassays showed strong inhibition, supporting its use in organic weed management (Anwar *et al*. 2017). Field studies demonstrated that its increasing density significantly reduced wheat yield and yield-related parameters. Yield losses increased sharply as weed density exceeded 20 plants/m², establishing this as a critical management threshold for minimizing crop loss due to its competition with toothed dock (Waheed *et al*. 2017). Allelochemicals are released through leaching, volatilization, leaf litter, and root exudation. Both aqueous and leaf powder extracts reduced radicle and plumule growth in wheat, maize, and sunflower up to 82%, confirming strong allelopathic suppression. These findings support the practical application of toothed dock extracts for natural weed control in sustainable agriculture (Anwar 2018).

CONCLUSIONS

R. dentatus stands out as a versatile medicinal plant with a rich history of traditional use across the world. Modern scientific investigations have validated many of its ethnomedicinal claims, demonstrating significant antibacterial, antioxidant, anti-inflammatory, antidiabetic, anticancer, and allelopathic properties. The plant contains diverse bioactive compounds, including flavonoids, phenolic acids, tannins, and anthraquinones. These are responsible for its broad spectrum of biological activities. Notably, extracts and isolated compounds from this plant have shown potent activity against multidrug-resistant bacteria, strong free radical scavenging capacity, and the ability to modulate inflammatory and metabolic pathways. Its combination with nanoparticle further amplifies its therapeutic potential, especially in antimicrobial and antioxidant applications. The plant also displays promising allelopathic effects, suggesting a role in sustainable agriculture as a natural bioherbicide. Despite these promising findings, further research is warranted to standardize extraction methods, clarify mechanisms of action and conduct comprehensive clinical trials to ensure efficacy and safety in humans. Overall, it offers significant potential as a source of novel natural products for pharmaceutical, nutraceutical and agricultural applications, bridging traditional knowledge with modern scientific validation.

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AUTHOR CONTRIBUTIONS

Fatma Hussain designed and supervised the research and final draft of the manuscript; Anza Rubab completed the research, Iqra Saleem assisted in write-up, rephrasing, and final draft preparation.

DATA AVAILABILITY

The data will be made available on a fair request.

ETHICS APPROVAL

Not applicable to this paper.

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CASE REPORT

A Case Report of Non-Classical Congenital Adrenal Hyperplasia of a Two-Year-Old Male Child

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METADATA

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Precocious puberty
Hydrocortisone therapy

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https://doi.org/10.63793/ISRE/0020

ABSTRACT

Background: Non-Classical Congenital Adrenal Hyperplasia (NCCAH) is a relatively common autosomal recessive disorder characterized by partial deficiency of 21-hydroxylase enzyme, resulting in excessive adrenal androgen production. The patient history included a high risk of supported pregnancy with growth injections and prior miscarriage.
Objective: This case report presents a rare early-onset of NCCAH in a 2-year-old male child who was brought to the endocrinology emergency department with premature pubic hair development and increased penile length. The objective was to find out the cause of this abnormal condition and find a clinical measure to arrest the condition.
Methodology: Based on clinical features and biochemical findings, a diagnosis of NCCAH was made. Hormonal therapy with oral hydrocortisone was initiated.
Results: Laboratory investigations disclose elevated levels of luteinizing hormones, ACTH, 17-hydroxyprogesterone, progesterone, and testosterone, while other hormonal and imaging studies were within normal range. Hormonal therapy with oral hydrocortisone led to partial improvement in androgen levels over a 3-month follow-up.
Conclusion: This case highlighted the need for early recognition of atypical presentation of NCCAH to prevent complications such as precocious puberty, compromised adult height, and fertility issues by timely therapeutic interventions.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive endocrine condition that affects cortisol production. The syndrome is caused by reduced activity of cortisol-producing enzymes, which results in prolonged adrenocorticotropic hormone (ACTH) stimulation of the adrenal cortex and accumulation of steroid precursors upstream of the enzymatic block (Claahsen-van der Grinten *et al*. 2022). CAH has been separated into classic and non-classic (NC) variants. The current research indicates that polymorphisms in the *CYP21A2* gene and their phenotypic expression are their main cause. In the classic type, enzyme activity is significantly decreased or missing, limiting cortisol production and resulting in newborn symptoms (Claahsen-van der Grinten *et al*. 2022). Non-classic CAH (NCCAH), also known as late-onset CAH, is the most prevalent autosomal recessive endocrine disorder. It is caused by partial 21-hydroxylase activity (about 20–50% of normal), which is adequate to sustain important cortisol and aldosterone activities; thus, hormone replacement is often needed. However, due to low cortisol levels, ACTH secretion is not controlled, resulting in adrenal hyperplasia and hyperandrogenism (Podgórski *et al*. 2018).

Additionally, 21-hydroxylase deficiency accounts for approximately 95% of CAH cases and can present as either the classic (salt-wasting or simple virilizing) or non-classic phenotypes. The remaining cases are primarily caused by 11β-hydroxylase or 3β-hydroxysteroid dehydrogenase deficits, in both classic and non-classic forms. In rare cases, defects in 17α-hydroxylase/17,20-lyase or cholesterol desmolase can lead to serious clinical problems (Piróg *et al*. 2024).

Mutations in *CYP21A2* range from complete loss to partial retention of enzyme function, with the majority resulting from gene conversion events between the functional gene (*CYP21A2*) and its highly similar pseudogene

(*CYP21A1P*). Functional testing show residual activity of 0–5% in severe mutations (Adriaansen *et al*. 2022). According to Kurtoğlu and Hatipoğlu (2017), classical CAH affects 1 in every 15,000–20,000 live births, while NCCAH affects 1 in 200 Caucasians and 1 in 100 of the general population.

The disease is more prevalent among Ashkenazi Jews (1 in 27), Hispanics (~1 in 40), Slavs (1 in 50), and Italians (1 in 300) (Macut *et al*. 2019). According to the original clinical criteria, NCCAH symptoms develop after the age of five years. Females are born without genital ambiguity, but both sexes can develop indications of androgen excess at any time throughout postnatal life. Delayed menarche is prevalent in adolescent females, and secondary amenorrhea can occur in young women (Auer *et al*. 2023).

Female patients may also experience hirsutism, oligomenorrhea, or polycystic ovary, while afflicted males may infrequently present with oligospermia. Untreated people of both sexes may develop small adult height, insulin resistance, and impaired fertility. Boys frequently experience premature pubertal development, precocious puberty, acne, and fast growth. Laboratory results frequently show elevated 17-hydroxyprogesterone, increased ACTH, and excessive luteinizing hormone (LH) release. Genetic testing is recommended for all CAH patients, including parents and siblings. NCCAH patients had an increased risk of testicular adrenal rest tumors, cardiovascular morbidity, and infertility (Muthusamy *et al*. 2010).The treatment of 21-hydroxylase deficiency began in the 1950s. Glucocorticoid replacement therapy restores insufficient cortisol while suppressing excess ACTH, lowering adrenal androgen synthesis. Hydrocortisone is the ideal replacement for 21-OHD, 11β-OHD, and 17α-hydroxylase deficits due to its favorable physiologic profile and lower risk of side effects (Muthusamy *et al*. 2010). The treatment of 21-hydroxylase deficiency began in the 1950s. Glucocorticoid replacement therapy restores insufficient cortisol while suppressing excess ACTH, lowering adrenal androgen synthesis. Hydrocortisone is the ideal replacement for 21-OHD, 11β-OHD, and 17α-hydroxylase deficits due to its favorable physiologic profile and lower risk of side effects (Muthusamy *et al*. 2010).

The medicine is commonly provided orally in divided daily doses (10–20 mg/m²/day) to maintain steady hormone levels and decrease androgens. Families receive emergency injectable hydrocortisone kits (50 mg for youngsters and 100 mg for older people). In situations of poor response, doses may be increased to 20–30 mg/m²/day or switched to more potent, longer-acting synthetic glucocorticoids such as prednisone or dexamethasone; cautious titration is required to avoid overtreatment (Finkielstain *et al*. 2012).

CASE PRESENTATION

Here is a case presentation of 2-year-old child who presented in the emergency to Faisalabad Diabetic and Endocrinology Centre (F-DEC) with the symptoms of pubic hair (4 cm) growth over the last 7 days. Physical examination indicates an

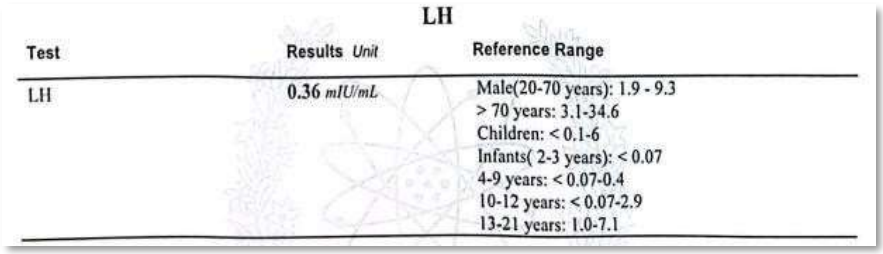
Fig. 1: Growth of pubic hairs (vellus hairs)

Fig. 2: Increased Penile Length

increased penile length of 7 cm that is too high according to his age, and this can be troublesome in the future, because the normal flaccid length in an adult male is 8.7 cm (Fig. 1–17). Clinical findings include the weight of the patient was 14 kg, height was 92 cm, and after laboratory analysis, the patient was diagnosed with non-classical congenital adrenal hyperplasia. There was no family history of any genetic cause; neither the father nor the mother had any disease. However, the mother had one miscarriage before this child during the first trimester, and the cause was unknown. The fetus showed no growth at all, which led to the miscarriage. About seven months later, the mother conceived again, and during the first month of pregnancy, she was given growth-supporting injections of Hydroxyprogesterone Caproate-Estradiol Valerate, four injections in total, administered once a week. This was considered an endangered pregnancy. The patient has eyesight issues, mental health was normal, he was socially active and there is growth of hair on the back of the patient. He was on hormonal therapy, taking Tab Hydrocortisone (10 mg) BD and some multivitamins.

DISCUSSION

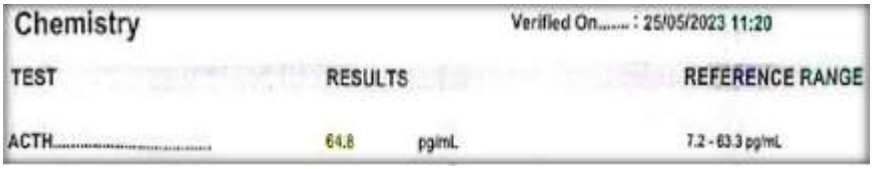
Non-Classical Congenital Adrenal Hyperplasia (NCCAH) is a common autosomal recessive endocrine disorder resulting from partial 21-hydroxylase deficiency. Unlike the classical older children, point to early onset virilization, which can occur even in non-classical form if androgen levels are remarkably high. Such presentations are not common and often overlooked due to the milder nature of NCCAH compared to classical forms. The absence of family history



LH

Test	Results *Unit*	Reference Range
LH	0.36 *mIU/mL*	Male(20-70 years): 1.9 - 9.3 > 70 years: 3.1-34.6 Children: < 0.1-6 Infants(2-3 years): < 0.07 4-9 years: < 0.07-0.4 10-12 years: < 0.07-2.9 13-21 years: 1.0-7.1

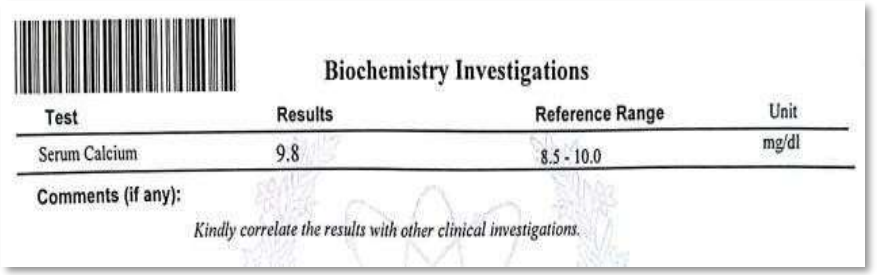
Fig. 3: Showing an elevated level of luteinizing hormone in a patient than normal range



Chemistry — Verified On..... : 25/05/2023 11:20

TEST	RESULTS		REFERENCE RANGE
ACTH.....	64.8	pg/mL	7.2 - 63.3 pg/mL

Fig. 4: Showing elevated level of adreno-corticotropic hormone



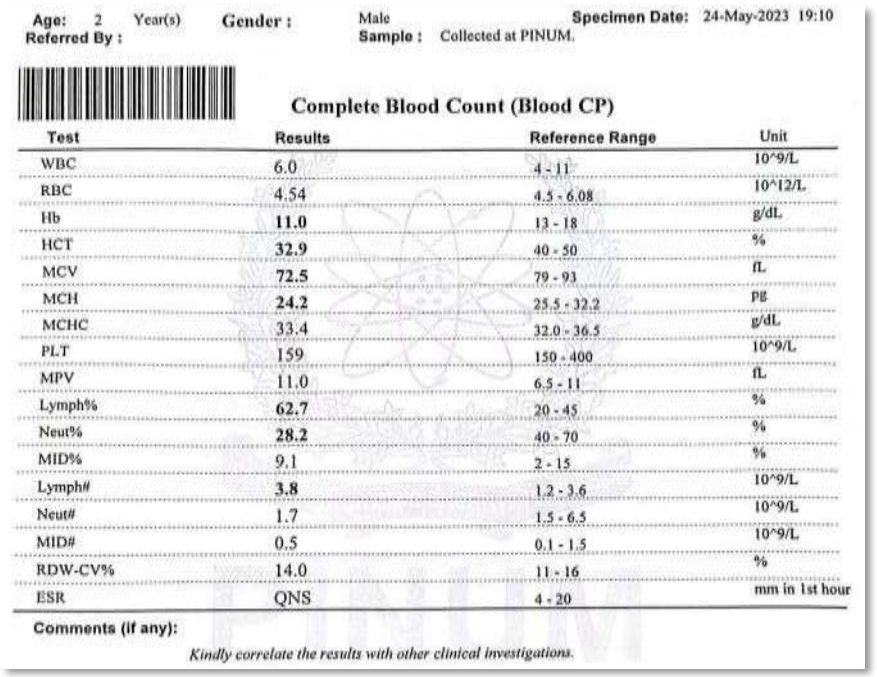
Biochemistry Investigations

Test	Results	Reference Range	Unit
Serum Calcium	9.8	8.5 - 10.0	mg/dl

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 5: Normal serum calcium level



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at PINUM.

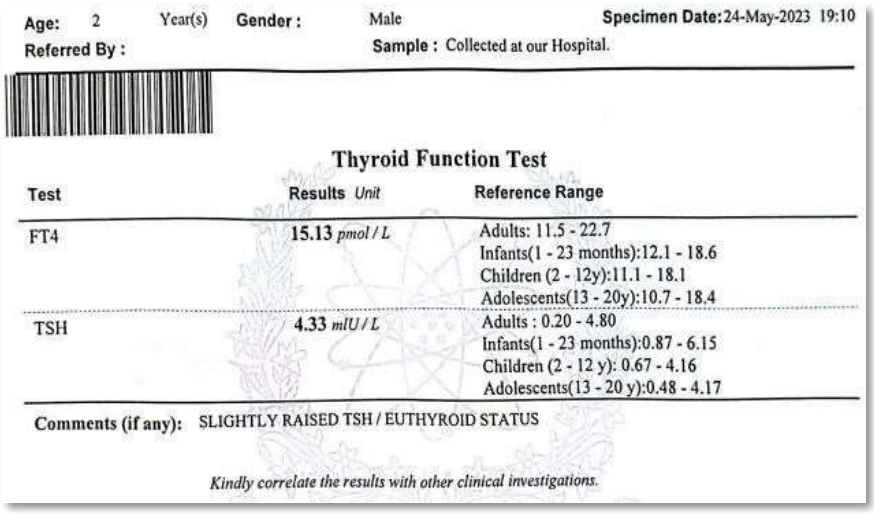
Complete Blood Count (Blood CP)

Test	Results	Reference Range	Unit
WBC	6.0	4 - 11	10^9/L
RBC	4.54	4.5 - 6.08	10^12/L
Hb	**11.0**	13 - 18	g/dL
HCT	**32.9**	40 - 50	%
MCV	**72.5**	79 - 93	fL
MCH	**24.2**	25.5 - 32.2	pg
MCHC	33.4	32.0 - 36.5	g/dL
PLT	159	150 - 400	10^9/L
MPV	11.0	6.5 - 11	fL
Lymph%	**62.7**	20 - 45	%
Neut%	**28.2**	40 - 70	%
MID%	9.1	2 - 15	%
Lymph#	**3.8**	1.2 - 3.6	10^9/L
Neut#	1.7	1.5 - 6.5	10^9/L
MID#	0.5	0.1 - 1.5	10^9/L
RDW-CV%	14.0	11 - 16	%
ESR	QNS	4 - 20	mm in 1st hour

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 6: Complete blood count (CBC) analysis of the patient



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

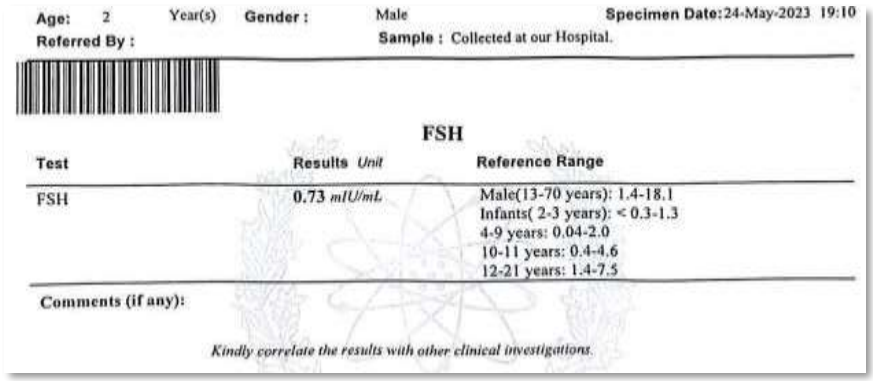
Thyroid Function Test

Test	Results *Unit*	Reference Range
FT4	**15.13** *pmol / L*	Adults: 11.5 - 22.7 Infants(1 - 23 months):12.1 - 18.6 Children (2 - 12y):11.1 - 18.1 Adolescents(13 - 20y):10.7 - 18.4
TSH	**4.33** *mIU / L*	Adults : 0.20 - 4.80 Infants(1 - 23 months):0.87 - 6.15 Children (2 - 12 y): 0.67 - 4.16 Adolescents(13 - 20 y):0.48 - 4.17

Comments (if any): SLIGHTLY RAISED TSH / EUTHYROID STATUS

Kindly correlate the results with other clinical investigations.

Fig. 7: Thyroid function test, indicating normal level of Free Thyroxin 4 (FT4) and milder elevated level of Thyroid Stimulating Hormone (TSH) in infants



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

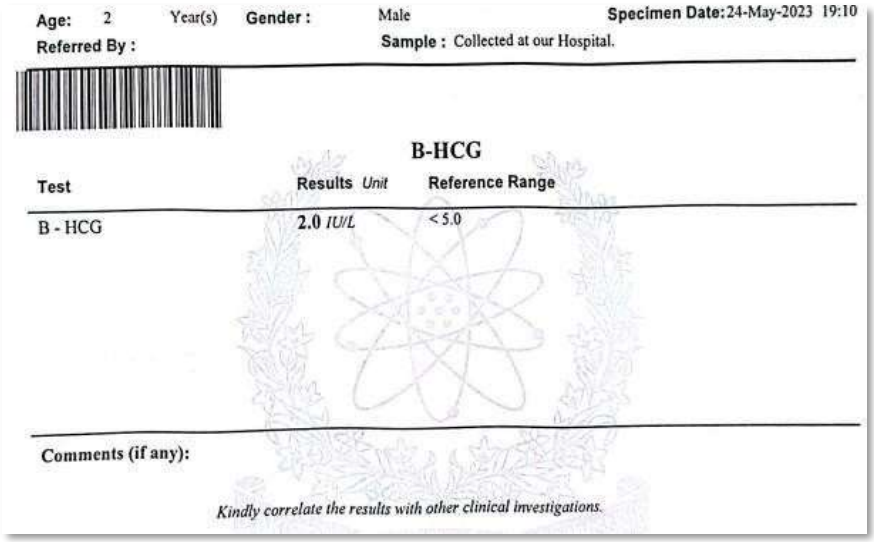
FSH

Test	Results *Unit*	Reference Range
FSH	**0.73** *mIU/mL*	Male(13-70 years): 1.4-18.1 Infants(2-3 years): < 0.3-1.3 4-9 years: 0.04-2.0 10-11 years: 0.4-4.6 12-21 years: 1.4-7.5

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 8: Showing normal range of follicle follicle-stimulating hormone (FSH) in infants



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

B-HCG

Test	Results *Unit*	Reference Range
B - HCG	**2.0** *IU/L*	< 5.0

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 9: Lab analysis showing normal value of Beta-human Chronic Gonadotropin in Patient

Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

Progesterone

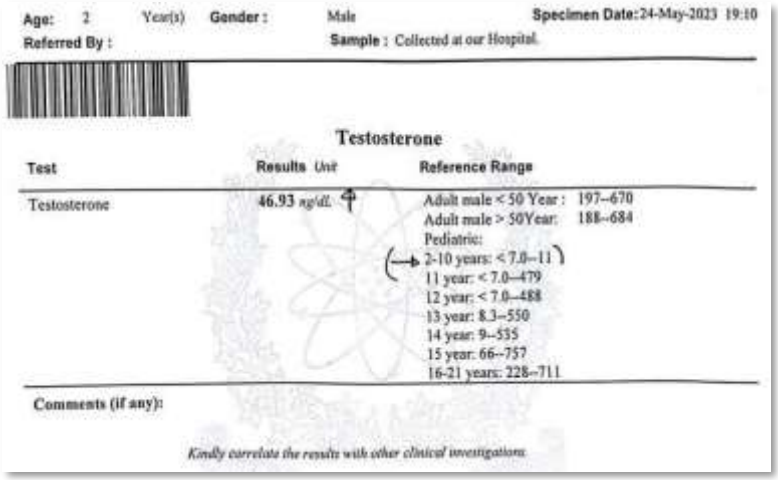
Test	Results Unit	Reference Range
Progesterone	11.23 ng/mL	0.28 - 1.22

Comments (if any):

Kindly correlate the results with other clinical investigations

17-oH-progesterone

Fig.10: Lab analysis shows an elevated level of progesterone analysis shows an elevated level of progesterone



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

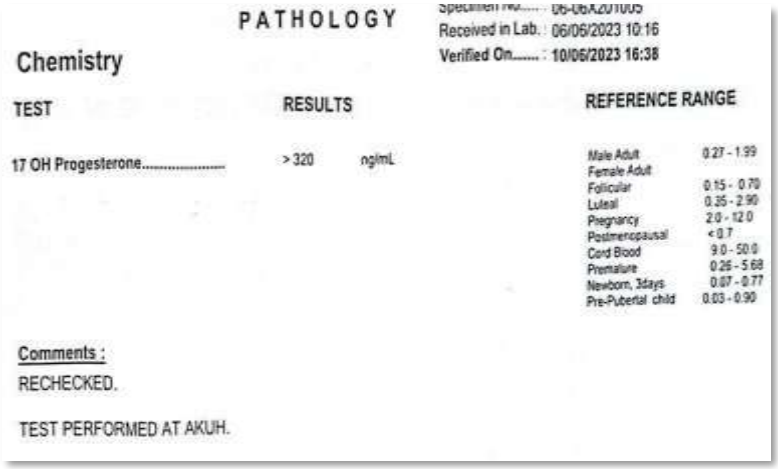
Testosterone

Test	Results Unit	Reference Range
Testosterone	46.93 ng/dL	Adult male < 50 Year : 197--670 Adult male > 50Year: 188--684 Pediatric: 2-10 years: < 7.0--11 11 year: < 7.0--479 12 year: < 7.0--488 13 year: 8.3--550 14 year: 9--535 15 year: 66--757 16-21 years: 228--711

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 11: Lab analysis shows an elevated level of testosterone



PATHOLOGY

Specimen Rec..... : 06-06A201005
Received in Lab. : 06/06/2023 10:16
Verified On..... : 10/06/2023 16:38

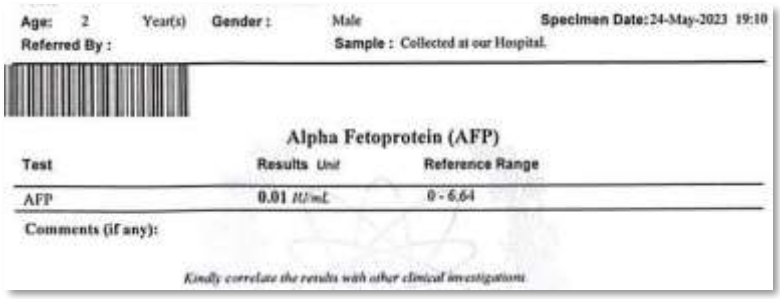
Chemistry

TEST	RESULTS		REFERENCE RANGE	
17 OH Progesterone.....	> 320	ng/mL	Male Adult	0.27 - 1.99
			Female Adult	
			Follicular	0.15 - 0.70
			Luteal	0.35 - 2.90
			Pregnancy	2.0 - 12.0
			Postmenopausal	< 0.7
			Cord Blood	9.0 - 50.0
			Premature	0.26 - 5.68
			Newborn, 3days	0.07 - 0.77
			Pre-Pubertal child	0.03 - 0.90

Comments :
RECHECKED.

TEST PERFORMED AT AKUH.

Fig. 12: Lab analysis shows an increased level of 17-hydroxy progesterone



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

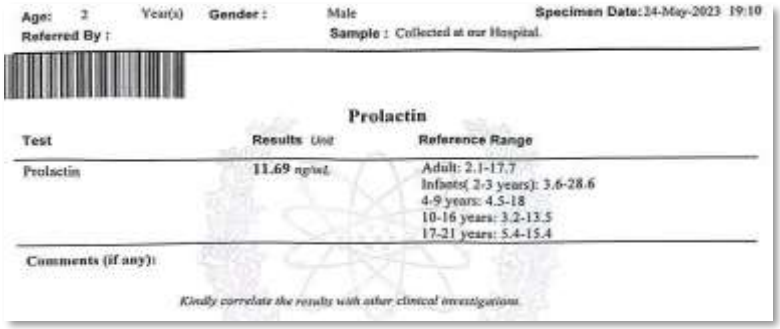
Alpha Fetoprotein (AFP)

Test	Results Unit	Reference Range
AFP	0.01 IU/mL	0 - 6.64

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 13: Lab analysis shows normal level of alpha fetoprotein



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

Prolactin

Test	Results Unit	Reference Range
Prolactin	11.69 ng/mL	Adult: 2.1-17.7 Infants(2-3 years): 3.6-28.6 4-9 years: 4.5-18 10-16 years: 3.2-13.5 17-21 years: 5.4-15.4

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 14: Normal range of prolactin hormone in patient

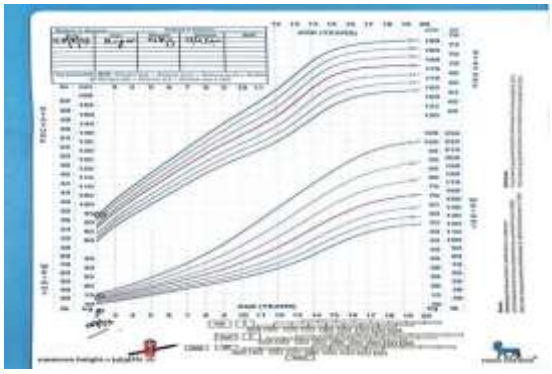


Fig. 15: Growth chart indicates height and weight relation

SCROTAL DOPPLER ULTRASOUND

Right testicle measures Volume 0.9ml
Left testicle measures Volume 1.0ml

Both testes are normal sized showing homogenous parenchyma and smooth contours. No focal mass lesion seen on either side.
Doppler indices of parenchymal arteries are normal.

Epididymii are of normal size and echotexture.

No hydrocele seen on either side. Scrotal wall is normal.
Both pampiniform plexus are unremarkable. No dilated venous plexus are appreciated on either side.

IMPRESSION:

- **Unremarkable Doppler Study**

Dr Hassan Bukhari

Fig. 16: Ultrasound report of the Scrotum region in the patient

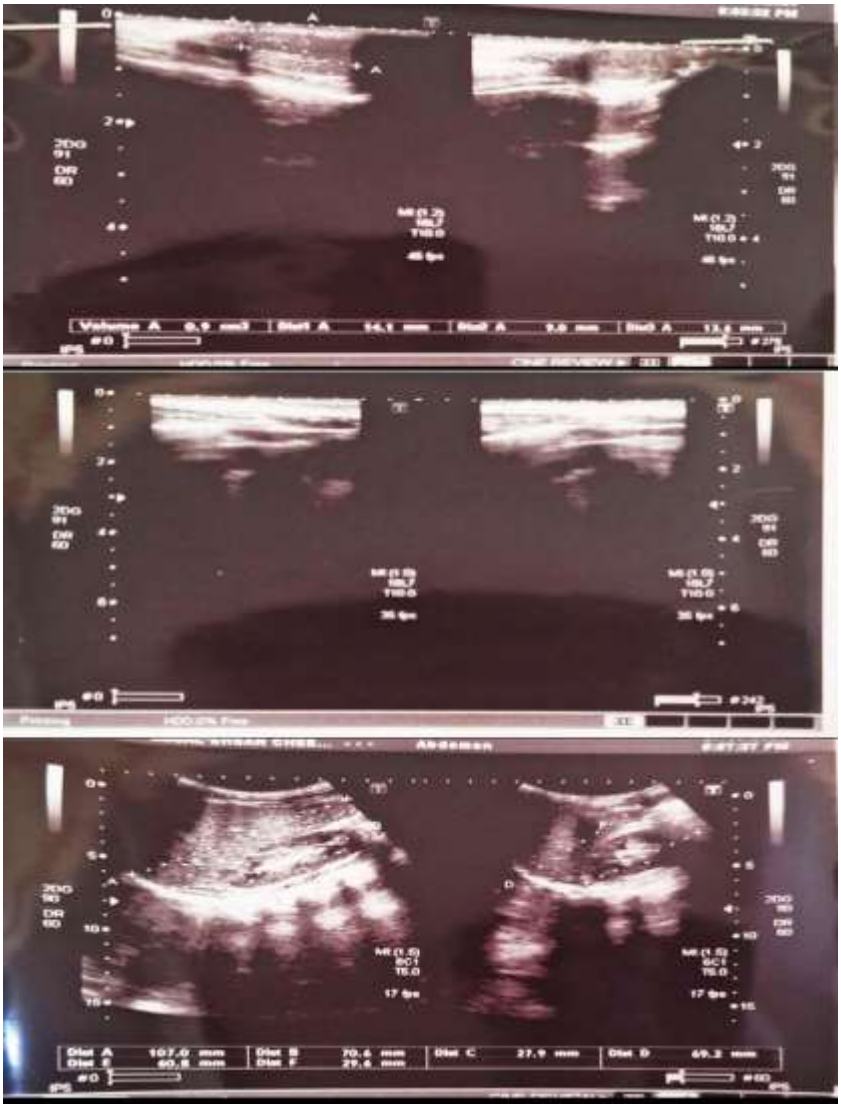


Fig. 17: Ultrasound image of the scrotum region in the patient

and the normal health status of both parents suggests a *de novo* carrier, indicating mutation or a recessive carrier state in one or both parents, which is consistent with an autosomal recessive inheritance pattern on CAH. The history of unexplained miscarriage in the first trimester may be coincidental, but it also raises the possibility of a previously affected fetus with a more severe phenotype or chromosomal abnormality (Finkielstain *et al*. 2012).

The administration of Hydroxyprogesterone Caproate and Estradiol Valerate during early pregnancy may have supported the gestation in this case, especially since it was labelled as an endangered pregnancy. However, there is limited evidence on whether these hormonal injections have any direct influence on fetal adrenal gland development. Elevated androgen levels in NCCAH result from partial 21-hydroxylase deficiency, leading to build-up of 17-OH progesterone and other precursors. In this case, early hormonal therapy with hydrocortisone has been initiated, which is recommended as first-line treatment to reduce ACTH secretion and adrenal androgen production. The psychosocial and physical impact of such early symptoms can be significant; hence, timely diagnosis and management are crucial (Auer *et al*. 2023). This case highlights the importance of considering NCCAH in the differential diagnosis of premature pubarche, even in the absence of a family history. It also points out the role of detailed perinatal history and early endocrinology evaluation in patients presenting with signs of androgen excess (Auchus and Arlt 2013).

AUTHOR CONTRIBUTIONS

Noor ul Ain designed and supervised the research and final draft of the manuscript; Fakhar Eman and Manahal Amjad completed the research, assisted in write-up, rephrasing, and

final draft preparation.

DATA AVAILABILITY

The data will be made available on a fair request.

ETHICS APPROVAL

Informed consent was obtained from the patient's family.

FUNDING SOURCE

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